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Applications of the Suzuki cross coupling reaction

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APPLICATIONS
OF THE
SUZUKI CROSS COUPLING REACTION

submitted by Kokovi Lawson Daku

for the degree of PhD

of the University of Bath

2003

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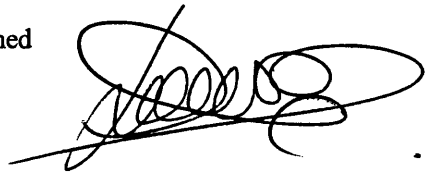
Signed  Date 7/11/2003

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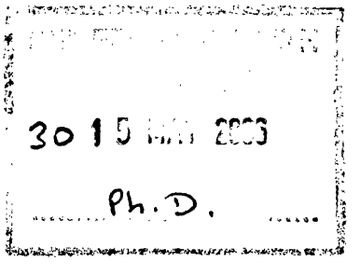
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Summary

The Suzuki reaction represents a versatile and powerful tool for the formation of C-C bonds. In comparison to other transition metal cross coupling reactions, the many advantages of the Suzuki reaction originate from the use of boronic compounds. This thesis reports mainly on the application of the supported aqueous phase catalysis (SAPC) or glass bead technology to the Suzuki cross coupling in aqueous media.

Chapter 1 reviews the mechanism, conditions and recent advances reported for the Suzuki cross coupling reaction.

Chapter 2 deals with the use of the supported catalyst. The first section reviews the advantages and disadvantages of heterogeneous catalysis, biphasic systems and describes the supported aqueous phase catalysis. The second section reports the reactivity of the supported catalyst using a readily available catalyst such as $Pd(PPh_3)_4$ for the coupling of various organohalides and boronic acids. The reactions were mainly carried out in aqueous media. Then the recycling of the catalyst and a comparison of the reactivity of unsupported $Pd(PPh_3)_4$ with the reverse phase glass bead catalysts were also investigated. In addition the use of the glass beads as sponge beads to remove palladium from aqueous solutions and the scaling up process for the synthesis of one compound were investigated. Finally, the subsequent sections briefly examine the reactivity of the normal phase glass bead, and the influence of ultrasound or heating on the Suzuki reactions in biphasic systems.

Chapter 3, 4, and 5 give respectively the general conclusion and future work, the experimental procedures used and references. Finally, the Annexes gives details of palladium calculation and list of the products.

Keywords: Suzuki cross coupling; glass bead technology; aqueous media.

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The entire group ... past and present (2000-2003).

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*NB: I know this word does not exist!!!

A Ma Famille …

" Um le dape na mi vevede to
ame siame la non sinsende
amon bada bada la d'jani, mia d'jani do gio ! "

Il n'y a que peu de mots assez forts pour exprimer à quel point votre support, votre affection, votre accessibilité, vos chauds réconforts et votre joie de vivre ont été cruciaux pour moi tout au long de cette thèse et plus encore … MERCI !

There are no words strong enough to express how much your support, love, and cheering were essential to me throughout this thesis and even more … THANKS !

Contents

)))	ultrasound
AA	atomic absorption
Ac	acetyl
aq.	aqueous
Ar	aryl
atm	atmosphere
bbim	1,3-di-*n*-butylimidazolium
9-BBN	9-borabicyclo[3.3.1]nonanyl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINAS	2,2'-*bis*(diphenylphosphino)methylene binaphthyl
br	broad
cat	catalyst
CI	chemical ionisation
CPG	controlled-pore glass
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	*N,N*-dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
DoM	directed ortho metalation
dppb	bis(diphenylphosphino)butane

dppe	bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	bis(diphenylphosphino)propane
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
FT-IR	Fourier transform infrared
h	hour
HPLC	high-performance liquid chromatography
LC/MS	liquid chromatography / mass spectroscopy
m	multiplet
Me	methyl
mg	milligram
min	minute
μL	microlitre
mol	mole
mp	melting point
m/z	mass / charge
NMP	*N*-methylpyrrolidone
NMR	Nuclear Magnetic Resonance

NORBOS	3,4-dimethyl-2,5,6-*tris*(*p*-sulfonatophenyl)-1-phosphanorborna-2,5-diene
PEG-PS	polyethylene glycol-polystyrene
PFNMe	[2-(diphenylphosphino)ferrocenyl]ethyl-*N*,*N*-dimethylamine
Phosphazene base	*tert*-butylimino-*tri*(pyrrolidino)phosphorane
Ph	phenyl
ppm	parts per million
Ref	reference
r.t.	room temperature
SAP	supported aqueous phase
SAPC	supported aqueous phase catalysis
Scav	scavenger
SLP	supported liquid phase
sp	sponge beads
Bu	butyl
TCSM	tethered complex on a supported metal
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TOF	turnover frequency
Tol	tolyl
TON	turnover number
TPP	triphenylphosphine
TPPMS	monosulfonated triphenylphosphine
TPPDS	disulfonated triphenylphosphine

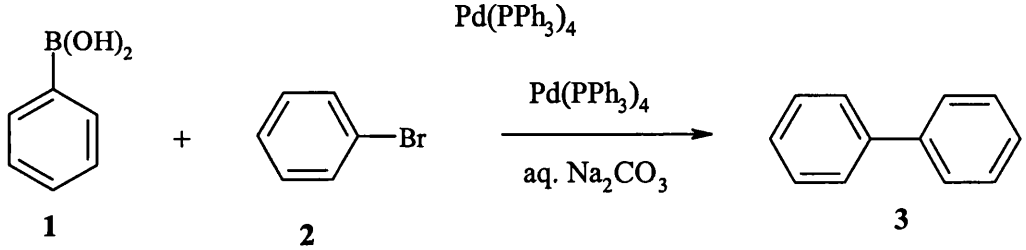
TPPTS	trisulfonated triphenylphosphine

The Suzuki Cross Coupling Reaction

The catalysis of organic reactions by soluble metal complexes, such as rhodium, platinum, palladium or ruthenium, has become a major synthetic tool. In particular, such complexes have been used for the formation of C-C bonds, which represents an important aspect of organic synthesis. During the past few decades there have been many developments resulting in a large variety of methods for the formation of this bond. An example is the palladium catalysed cross coupling of organometallics (Mg, Li, Cu, Zn, Sn and B) with organic electrophiles.

1.1 The Suzuki reaction[1,2]

The Suzuki coupling, Suzuki-Miyaura coupling or simply the Suzuki reaction is the cross coupling of organoboron derivatives with electrophiles in the presence of a palladium catalyst and a base. The reaction generally allows the cross coupling between a large variety of organohalides or triflates (1 equivalent) with organoboranes, organoboronic acids or esters, in the presence of a catalyst such as $Pd(PPh_3)_4$ or palladium(II) complexes (for example $PdCl_2$ and $Pd(OAc)_2$) with phosphines or other non-phosphines as added ligands, to yield the cross coupling product. A basic example is given in Scheme 1. The cross coupling of phenylboronic acid **1** with bromobenzene **2** gave the biphenyl **3** after 6 hours in good yield (88%).



- Scheme 1 -

Why has this reaction become so popular?

When Suzuki reported the first reaction, the use of organoboron derivatives was and is still a major advantage over other cross coupling reactions. In general organometallic compounds such as Grignard reagents, organolithium or organocopper compounds do not tolerate sensitive functionalities, are air and / or moisture sensitive and can be toxic as for example organotin reagents. By contrast the organoboron derivatives are generally:

(i) non-air, non-moisture sensitive

(ii) non-toxic and therefore no toxic waste

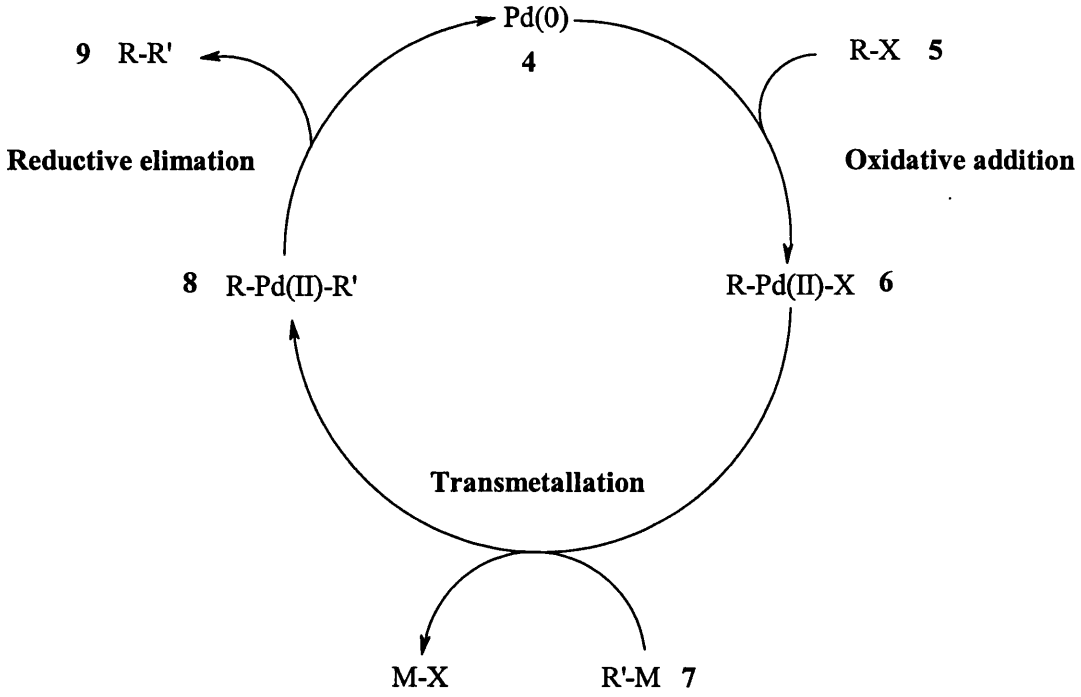
(iii) commercially available

(iv) tolerant of water

All of these qualities make the Suzuki reaction a powerful and versatile tool for the formation of C-C bonds.

1.2 Mechanism of the Suzuki reaction[2]

The catalytic cycle for the cross coupling of palladium metal with organo-magnesium (Kharasch reaction), organo-zinc (Negishi reaction), organo-tin (Stille coupling) or organo-boron compounds (Suzuki reaction) is similar, as shown in Scheme 2, where the ligands of the complex are omitted for clarity.[3]

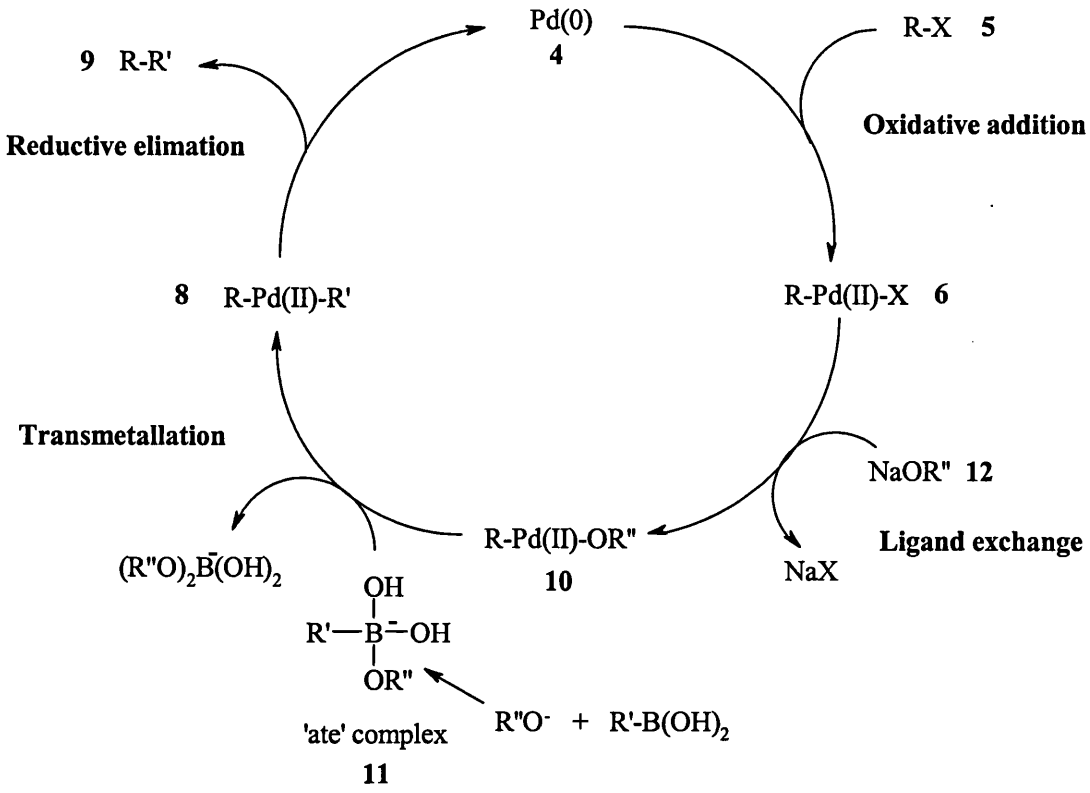


- Scheme 2 -

The first step of this catalytic cycle is the oxidative addition of the organohalide R-X **5** to the activated Pd(0) complex **4** to give the palladium(II) intermediate **6**, R-Pd(II)-X. The next step is the transmetallation of compound **6** with the organometallic reagent R'-M **7**, to afford complex **8**, R-Pd(II)-R'. After its *trans* to *cis* isomerisation, the reductive elimination gives the coupling product R-R' **9** and the catalyst is regenerated.

The most noteworthy difference of the Suzuki reaction in comparison to all other cross coupling reactions is the requirement of base. Two equivalents of base such as NaOR are used in the reaction. One equivalent is necessary to activate the boronic acid or ester. The base coordinates to the boron atom to give the activated form of the organoboron compound, the 'ate' complex intermediate **11**,[4,5] which then reacts in the catalytic cycle, Scheme 3.

The role of the second equivalent of base is still not fully understood.



- Scheme 3 -

Suzuki *et al* demonstrated the role of the second equivalent of base for the coupling of 1~alkenylboron compounds with alkenyl halides.[6] In this case the second equivalent of base would activate the palladium intermediate **6** by exchange of ligands to give the intermediate **10** (ligand exchange), which would facilitate the transmetallation with organoboranes. The halide in the coordination sphere of the palladium complex is exchanged by the base RO^- **12**, Scheme 3. However Aliprantis and Canary have analysed the reaction between 3-bromopyridine and various phenylboronic acids and they have only observed the intermediates **6** and **8** by electrospray ionisation mass spectroscopy. [7] It is not yet obvious in many reactions which process is predominant, and although Suzuki *et al* have never investigated the mechanism of aryl-aryl coupling reaction, they believe

that there is a strong possibility that the intermediate **10** is also formed in this case and generally.[8,9]

After the ligand exchange to give compound **10**, the transmetallation occurs, the activated boronic species **11** reacts with the intermediate **10** and allows the transfer of the organic group R' to the coordination sphere of the palladium specie to give the intermediate **8** R~Pd(II)-R'. Finally, this last compound undergoes a reductive elimination to form the cross coupling product and the palladium catalyst is regenerated as explained previously, Scheme 2.

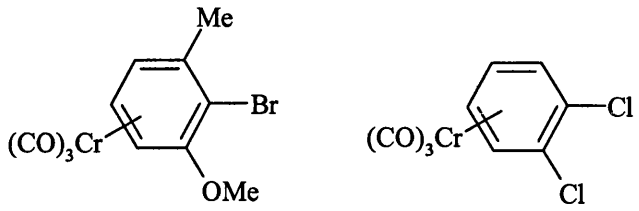
1.3 Further advances in Suzuki Coupling Reactions

Various improvements to the Suzuki reaction have been reported in the past two decades to allow the development of a wide range of bases, organoboron compounds or palladium catalysts and ligands depending on the structure of the reagents involved in the reaction. There are many parameters; therefore each of the following sections will only focus on the main achievements.

1.3.1 Organohalides

Among all of the possible organohalides, aryl or aromatic halides have been the most widely studied due to their wide range of applications. For example, compounds that contain a biaryl linkage have a diverse spectrum of applications, ranging from material science to pharmaceuticals. The general relative reactivity of organohalides decreases in the order I > Br ≥ TfO >> Cl. Also aryl and 1-alkenyl halides that are activated by electron withdrawing groups are more reactive than those with donating groups. However, there are a few examples using arene chromium tricarbonyl complexes, where the coupling of electron rich aryl halides and even some dichlorinated rings with boronic

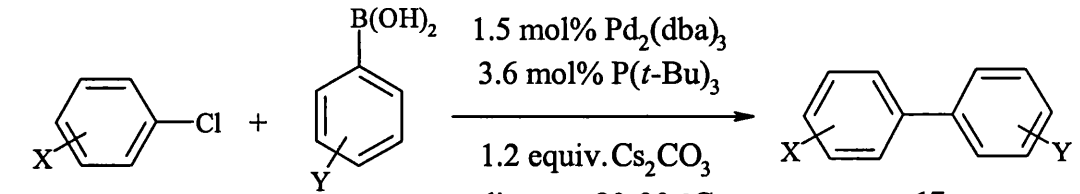
acids, such as compound **13** and **14**, Figure 1, was achieved in good yields (43% - 96%).[10,11]



13 **14**

- Figure 1 -

Usually aryl chlorides are not good candidates for the Suzuki cross coupling. The limitation to the reaction is mainly due to their low reactivity towards the oxidative addition step.[12] But recently, Fu *et al* have developed a general method for the cross coupling of aryl chlorides. They have reported that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyses the coupling of a wide array of aryl chlorides **15** with arylboronic acid **16** in the presence of caesium carbonate to yield the corresponding biaryl **17** in good yields (82-92%), Scheme 4.[13]



15 **16** **17**

X = COMe, Me, OMe, NH_2

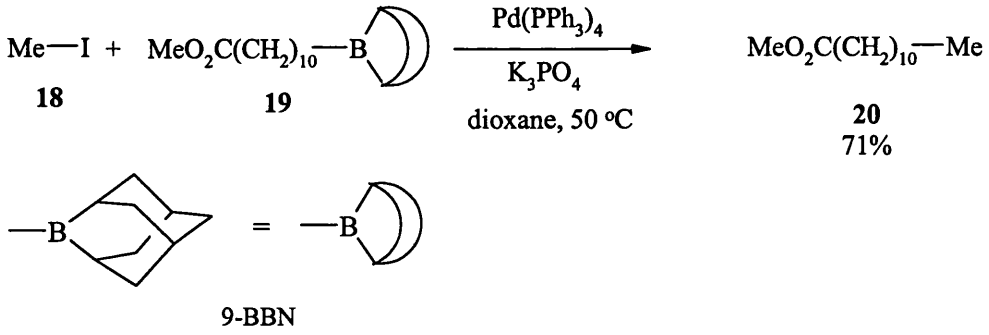
Y = CF_3, H, Me, OMe

82-92%

- Scheme 4 -

Some others examples of cross coupling with electron rich or poor aryl chlorides are also respectively reported by Buchwald *et al* and Shen *et al.*[14,15]

Although a wide variety of electrophiles, such as aryl, 1-alkenyl, benzyl, allyl, and alkynyl halides have been used for the palladium catalysed cross coupling reactions, the alkyl-alkyl coupling reaction is difficult.[2] Alkyl halides having β-hydrogens have a slow rate of oxidative addition to palladium(0) complexes and undergo a fast β-hydride elimination from σ-alkylpalladium intermediates in the catalytic cycle. However in the last decade the reaction of primary iodoalkanes with 9-BBN derivatives such as **19** in presence of $Pd(PPh_3)_4$ and K_3PO_4 have been found to give the corresponding coupling product **20** in good yields (50 – 60% in general and 71 % for iodomethane **18**), as shown in Scheme 5.[16]

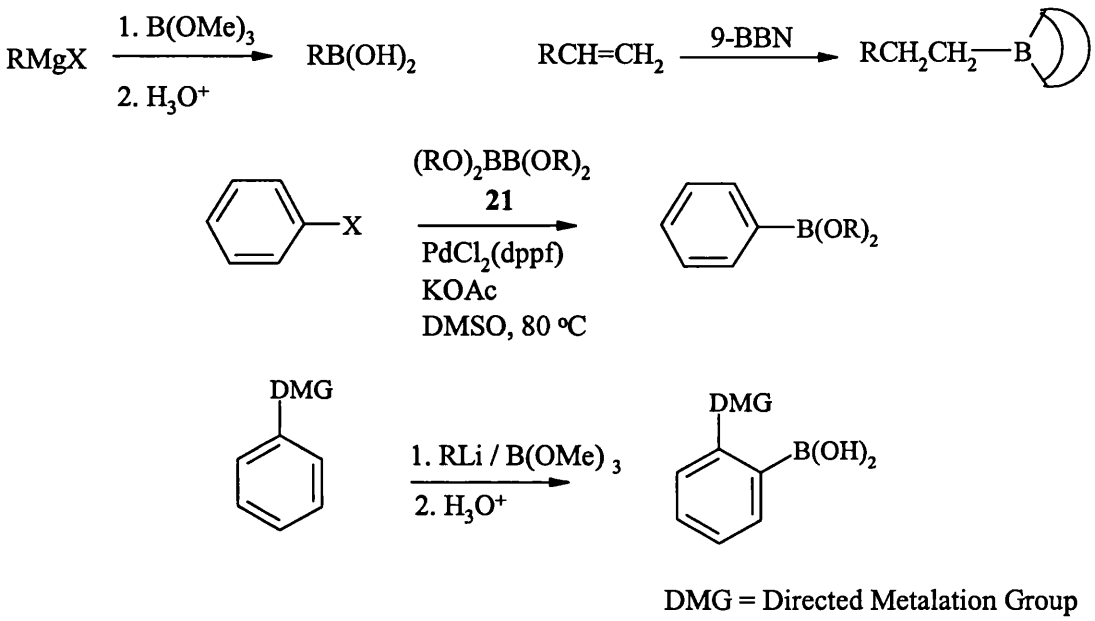


- Scheme 5 -

Finally, iodocyclopropanes have also been reported as good coupling partners in Suzuki reactions.[17,18]

1.3.2 Organoboron compounds

Alkenyl-alkenyl, aryl-aryl, and alkyl-alkenyl couplings have been investigated, partially due to the readily available boron compounds. Indeed, defined alkyl or alkenylboron reagents are available by hydroboration of alkenes or alkynes respectively.[19-21] Arylboronic acids and esters can be prepared readily from aryl Grignard, aryl lithium reagents or cross coupling reaction with alkoxyldiboron **21**, Scheme 6.[22,23]

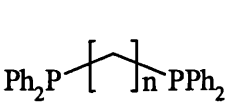


- Scheme 6 -

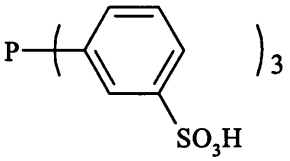
Also, Snieckus *et al* have reported the use of a directed ortho metalation procedure to obtain arylboronic acids, Scheme **6**, and they have demonstrated that the combination of the directed ortho metalation with the cross coupling is a powerful tool for the synthesis of natural products.[24]

1.3.3 Catalysts

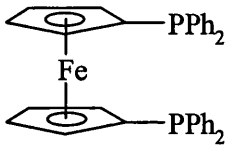
A very wide range of palladium(0) catalysts or precursors can be used for the cross coupling reaction. The most conventional palladium sources are $Pd(PPh_3)_4$, $Pd(Cl)_2$ and $Pd(OAc)_2$. Various phosphines or non-phosphine ligands are also added to the palladium(II) sources. Although the diversity of ligands used is vast in the Suzuki cross coupling, the most commonly used ones are shown below in Figure 2.



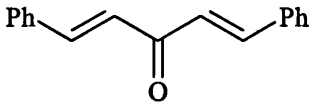
n = 2 : dppe **22**
3 : dppp **23**
4 : dppb **24**



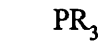
TPPTS
25



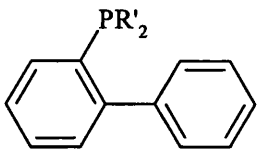
dppf
26



dba
27



R= Ph **28**
Cy **29**
t-Bu **30**

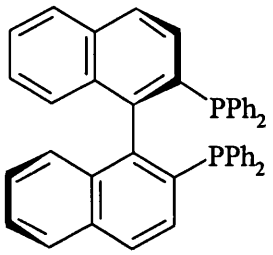


R' = Cy **31**
t-Bu **32**

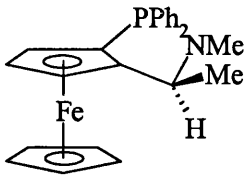
- Figure 2 -

The right choice of the catalyst system (Pd + ligand(s)) can be essential for reactivity. For example, TPPTS **25** and other derivatives are used to perform cross coupling in aqueous media;[25] dba **27** or dppf **26** are particularly used for the coupling of aryl chlorides;[26] also the palladium catalysts formed from ligands **31** and **32** show high activity at low catalyst loading (down to 10^{-6} mol%) for the coupling of various aryl bromides or chlorides at room temperature;[27,28] dppe **22**, dppb **24** and obviously triphenylphosphine **28** (and others phosphines) are used for a diverse range of cross coupling reactions.[29] Enantiomerically

enriched ligands such as (R)-(+)-BINAP **33** and (S)-(R)-PFNMe **34**, Figure 3, have been used to realise some asymmetric Suzuki cross coupling to give binaphthalene derivatives in up to 85% ee, when ligand (S)-(R)-PFNMe is used.[30]



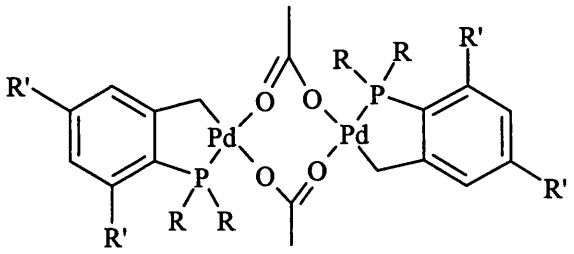
(R)-(+)-BINAP
33



(S)-(R)-PFNMe
34

- Figure 3 -

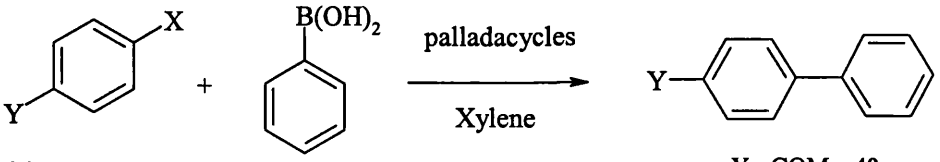
More recently, some new palladium catalysts generally called palladacycles have been reported. These catalysts were initially developed for the Heck reaction, where higher activity than for their standard phosphine palladium counterparts was observed. Indeed, for the first time turnover numbers above 1,000,000 were observed in the Heck coupling of *n*-butylacrylate with the electronically activated 4-bromoacetophenone in the presence of the palladacycle catalyst **35**, Figure 4.[31] With the increasing importance of unsymmetrical substituted biaryl derivatives for example as drug intermediates, Beller *et al* have first reported the attempts to employ the palladacycles **35** and **36** for the Suzuki coupling.[32]



R = *o*-tolyl , R' = H **35**
R = mesityl, R'= Me **36**

- Figure 4 -

After optimisation of the reaction conditions, a yield of 74% and a turnover number of 74,000 was reported for the coupling of phenylboronic acid **1** with 4-bromoacetophenone **37** in presence of only 0.001 mol% of palladacycle **35**, entry 1, Table 1. Also, since applications of chloroarenes are particularly attractive from an industrial point of view (chloro-compounds being cheaper than bromo- or iodo- compounds) the coupling of 4~chloroacetophenone **38** has been investigated, entries 2 and 3 Table 1. The desired product **40** was isolated with a yield of 82% and even when the amount of catalyst was reduced by a factor of ten, 21% of the product was still isolated and with a turnover number of 2,100.



Y= COMe X= Br **37**
Y= COMe X= Cl **38**
Y= OMe X=Br **39**

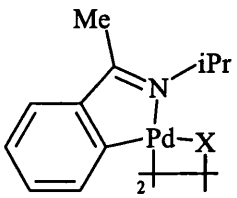
1

Y= COMe **40**
Y= OMe **41**

Entry	Y	X	Catalyst (%mol)	Yield (%)	TON
1	-COMe	Br	0.001	74	74000
2	-COMe	Cl	0.1	82	820
3	-COMe	Cl	0.01	21	2100
4	-OMe	Br	0.01	76	7600

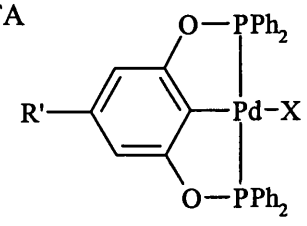
- Table 1 -

Although the coupling of 4-bromoacetophenone under these conditions is high, unfortunately for more electronically challenging substrates such as 4-bromoanisole **39**, entry 4, Table 1, a yield of 76% and a turnover number of only 7,600 was observed. Other palladacycle catalysts for the Suzuki reaction have been reported in the last decade since the first attempts by Beller. Also, Bedford has published a recent and complete review on the subject.[33] A few new palladacycles are shown in Figure 5.

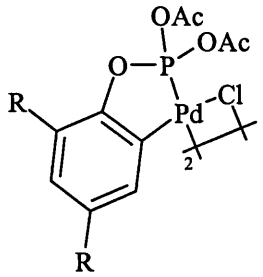


42

X= TFA



43



R= *t*-Bu

44

- Figure 5 -

For example, the catalytic activities of complexes **42, 43** and **44** for the cross coupling of 4-bromoacetophenone **37** with phenylboronic acid **1** under general conditions are shown in Table 2. A high turnover number of a million was observed in presence of only 0.0001 mol% of catalyst **44**, and the product is formed with 100% conversion.

X	Y	cat	%mol	Conversion (%)	TON	Ref
Br	COMe	**43**	0.001	92	92,000	[34]
Br	COMe	**44**	0.0001	100	1,000,000	[35]
Br	COMe	**42**	< 0.0001	84 (yield)	840,000	[36]

- Table 2 -

Finally, there are also a few examples of palladium free,[37] Pd/C or phosphine free cross coupling reactions.[38]

1.3.4 Bases

Many bases such as Na_2CO_3, NaOEt and NEt_3 have been employed in the Suzuki reaction and their influences on the coupling of different reagents have been studied.

Base(s)	For the coupling of	Ref
K_3PO_4	Organotriflates, alkyl iodates	16, 39
CsF, Cs_2CO_3	Aryl chlorides	13
Strong bases: NaOH, BaOH, KO^tBu, NaOEt	Sterically hindered aryl halides	40, 41
Weak base: Na_2CO_3	Non-sterically hindered aryl halides	1
Others	Diverse reagents	2

- Table 3 -

For instance, the aryl-aryl coupling of less sterically hindered aryl boronic acids gives generally better results using weak bases, whereas sterically hindered aryl boronic acids gives higher yields with strong bases. Also it was reported that in some cases the use of amines as bases could dramatically accelerate the reaction rate.[42] A succinct summary of the major bases and their uses is outlined in Table 3.

1.3.5 Other parameters

Other parameters among the reaction conditions, such as temperature or solvent can be varied to suit the appropriate coupling. There has been an emergence of reactions promoted by microwave or ultrasound (which cut down the reaction time),[43,44] using fluorous phase or using heterogeneous catalysis.[45]

1.3.6 Overview[2]

The scope of the palladium catalysed cross coupling reaction of the representative organoboron compounds with organic halides is summarised in Table 4.

	Alkyl-B	CH_2=$CHCH_2$-B	RCH=CH-B	Ar-B	R-C≡C-B
Alkyl-I	+	-	+	+	-
CH_2=$CHCH_2$X	-	-	+	+	-
RCH=CH-X	+	+	+	+	+
ArX	+	+	+	+	+
R-C≡C-X	-	-	+	+	-

+: Successful; -: unsuccessful

- Table 4 -

In summary the Suzuki cross coupling is a powerful tool for the cross coupling of a wide range of organohalides and organoboron compounds.

1.4 A few disadvantages

Although palladium is cheaper than other transition metals such as gold, the cost of this homogeneous catalysis would be still quite significant. So despite its huge advantages, the Suzuki cross coupling is still quite an expensive reaction to realise, especially in industry. In addition as for any transition metal reactions throughout a synthesis, palladium contamination of the products is an important issue especially for pharmaceutical purposes. Therefore the design of highly efficient supported recyclable catalysts is essential. The solid support would then help to decrease the metal leaching and ease the

separation of products and reagents, and the possible recycling would decrease the overall cost.

Suzuki Cross Coupling

Using

Glass Beads

2.1 Heterogeneous Catalysis

2.1.1 Introduction

Homogeneous transition metal catalyses are commonly used in organic synthesis. These catalysts are known to show high activities and selectivities under relatively mild conditions, especially for the synthesis of chiral compounds and with few by-products. These essential properties have emerged from the development of homogeneous catalysis over several decades. However, it has long been recognised that a limitation of homogeneous catalysis is the evident need for the separation of the catalytic system from the reaction mixture.[46] Depending on the catalytic system:

(i) the catalytic species can be expensive, e.g. rhodium complexes

(ii) the separation may not be as complete or cost-effective as desired

(iii) metal contamination in pharmaceutical products must be minimised

These reasons explain why homogeneous catalysis has been and is still underused by the fine chemical industry. An efficient separation is essential when the reaction products are to be used to generate drugs, as there is often a toxicity related to transition metal residues.

Thus, there have been many attempts to transpose well-established homogeneous catalysts to heterogeneous ones, and towards the design of a heterogeneous catalyst that would have a high activity and selectivity. In addition, catalysts of this nature would be economically viable, with simple separation and recovery steps, and would minimise the toxicity hazards due to contamination by traces of transition metal. Many of these methods are based on anchoring the ligands of the transition metal catalyst onto various solid supports, but they have often lacked success. The efficiency of the modified catalyst

is often suppressed due to its restricted mobility within the solid support, resulting from the anchoring method. Immobilisation using a 'liquid support' is to some extent a more successful mode. In this process two immiscible liquid phases are employed, where one contains the catalyst and the other the reagents and products. Such biphasic catalyses are becoming more and more popular, as new water-soluble organometallic catalyst complexes are introduced.

More recently, a supported catalysis called Supported Aqueous Phase Catalysis (SAPC), which combines a biphasic catalytic system with a solid support, was reported.[47] It has been described to bridge the gap between homogeneous and heterogeneous catalysis. The following sections will examine in more detail the areas mentioned above, in turn to exemplify the drive for the work on SAPC.

2.1.2 Homogeneous versus heterogeneous catalysis[48,49]

A homogeneous catalysis reaction is, by definition, one in which all reagents and the catalyst are present in the same phase. The catalyst is usually a well-defined single transition metal complex or a combination of discrete complexes. By contrast, in a typical heterogeneous catalysis one or more of the reagents are present as a solid state. Usually, the catalyst is anchored onto a solid support and the reactants are liquids or gases. The reaction then takes place at the phase interface. The strengths and weaknesses of homogeneous and heterogeneous catalysis are summarised in Table 5.

	Homogeneous catalysis	Heterogeneous catalysis
Activity (relative to metal)	high	variable
Selectivity	high	variable
Reaction conditions	mild	harsh
Service life of catalyst	variable	long
Sensitivity towards catalyst poisons	low	high
Diffusion problems	none	may be important
Catalyst recycling	expensive	easy
Variability of steric and electronic properties of catalysts	possible	not possible
Mechanistic understanding	possible	difficult

- Table 5 -

The solid-state nature of a heterogeneous catalyst system gives it certain advantages over its homogeneous counterpart. From a practical point of view the main benefit is the ease with which the catalyst or product can be separated from the reaction mixture, assuming the substrates or products are either liquids or gases. Such catalysts are easily recovered and generally have a high thermal stability. However heterogeneous catalysis also has some drawbacks, such as variable activity and selectivity, Table 5. This is mainly due to the fact that there are many different sites on the solid catalyst. Among all these different sites, it is possibly that only one type catalyse the desired reaction, at best the other types of sites do not get involved, at worst they may catalyse undesired side reactions. With homogeneous transition metal catalysts, there is generally only one type of active site, thus in terms of activity per metal centre, homogeneous catalysts are frequently more active, more selective and their mechanisms are easier to understand.

Although homogeneous catalysis holds many advantages, it remains underused as a result of the difficulties with the catalyst and products separation. In fact, today about 85% of processes in industry use heterogeneous catalysis.

2.1.3 Biphasic systems

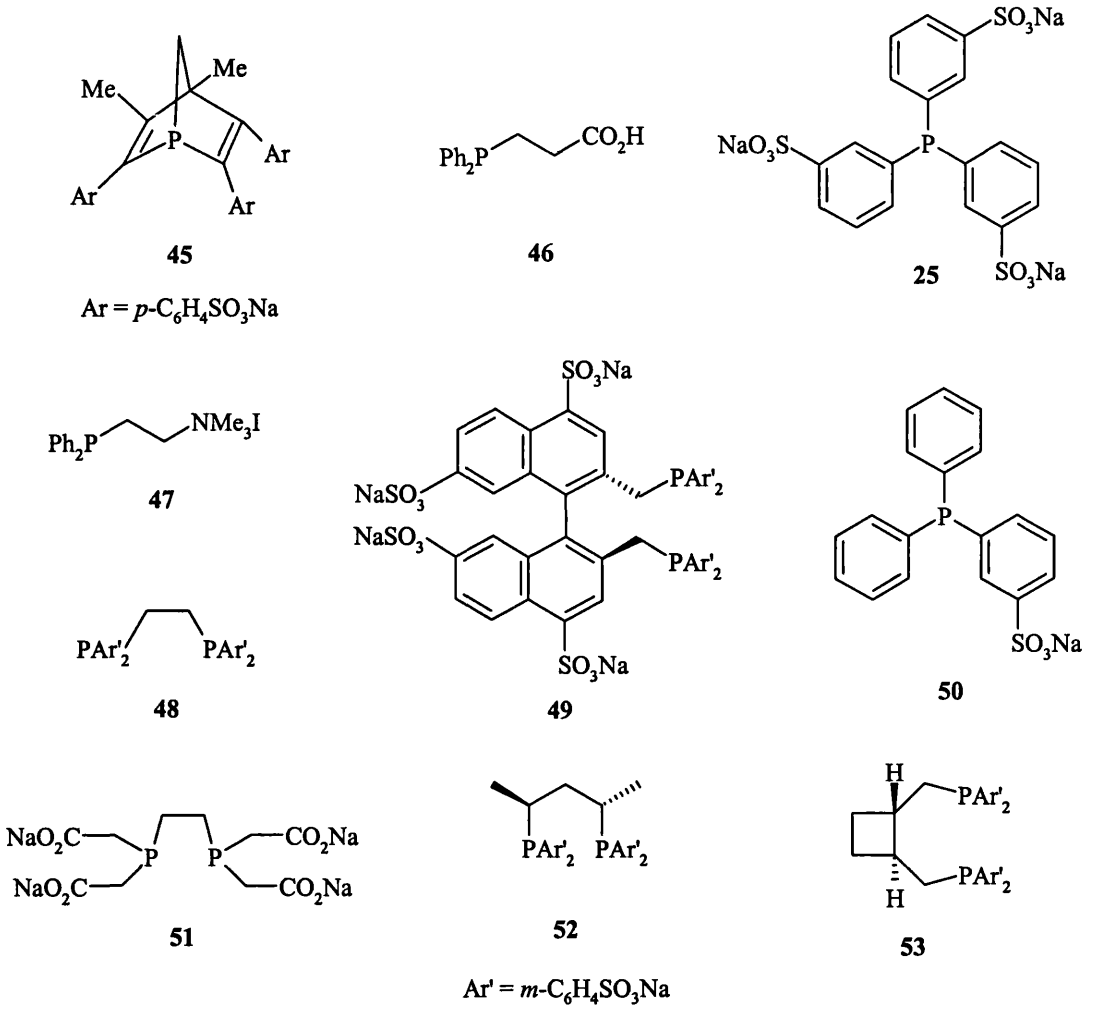
2.1.3.1 Introduction

As previously mentioned, the major disadvantage of homogeneous catalysis is the step of separation of the catalyst from the products. Frequently, the processes usually necessary to achieve the separation lead to thermal stress on the catalyst, which can cause its decomposition and / or deactivation. Biphasic catalysis using water-soluble ligands and their metal complexes has been undergoing a very rapid growth since the early 1980's with the development by Ruhrchemie / Rhône Poulenc of a biphasic hydroformylation process.[50,51] This system combines advantages of both homogeneous and heterogeneous catalysis, the complete separation of products and catalyst is generally simple and catalysts often exhibit high activity and selectivity. In addition, water is used as co-solvent, which is environmentally friendly. The water-soluble catalyst resides in the aqueous phase and reacts at the interface with the organic solvent containing the reagents and later the products.

2.1.3.2 Diversity of water-soluble ligands

Numerous transition metal complexes are stabilised by phosphorus-containing ligands. Therefore their adaptation into water-soluble ligands has been largely studied and hydrophilic phosphines now represent the largest class of water-soluble ligands. Polar functionalities such as carboxylate, ammonium, phosphonium, hydroxyl and particularly sulfonate groups have been used to tailor these ligands.

A few examples of water-soluble ligands are shown in Figure 6. The major class, which is the sulfonates, has been mostly used due to the high hydrophilicity of this group.



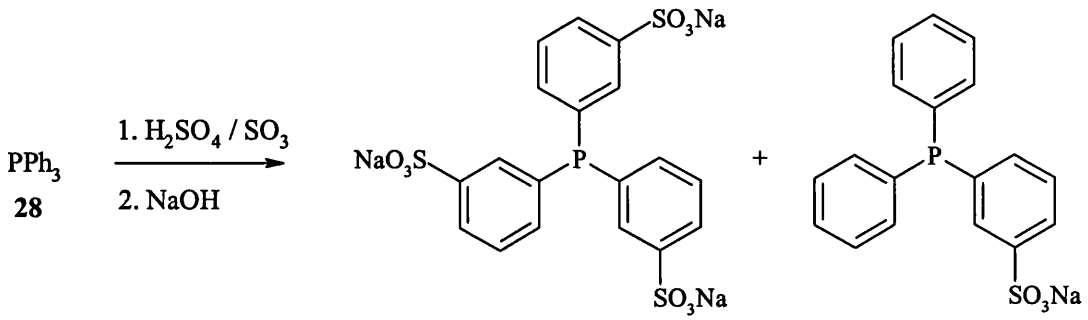
- Figure 6 -

Sulfonated phosphine ligands

One of the most widely used strategies for obtaining water-soluble ligands is the direct sulfonation of successful known aromatic ligands. An important example is the tri-sulfonation of triphenylphosphine **28** to give TPPTS **25**. This ligand has an incredible solubility in water of 1100 g per litre.[52]

- The "TPP-SO_3H family"

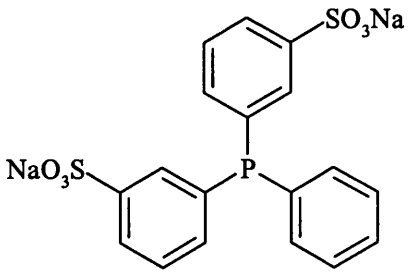
Generally, the sulfonation is achieved using oleum (SO_3, in concentrated H_2SO_4). Originally, this procedure gave mainly the monosulfonated ligand TPPMS **50**, Scheme 7.[53,54]



25 **50**

- Scheme 7 -

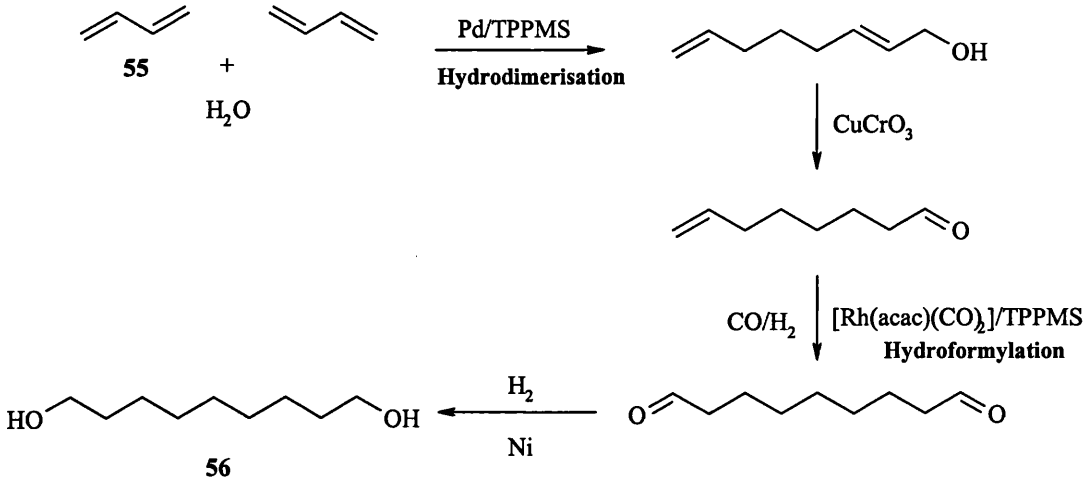
In 1976, Kuntz *et al* improved this process by prolonging the reaction time and achieved an adequate purity for industrial use by repeated precipitation of the product from a mixture of methanol and water.[52] Although the synthesis of TPPTS was available, the complexity and difficulties for obtaining the pure ligand are problematic. This is mainly due to the formation of phosphine oxides during the sulfonation. However it was reported that optimisation of the temperature, reaction time and oleum concentration can reduce this side reaction.[55,56] Besides, the introduction of the sulfonate group during the phosphine synthesis is a good alternative way to avoid the side reaction.[57,58] Apart from TPPTS and TPPMS, which are used on an industrial scale, the di-sulfonated derivative TPPDS **54** must also be mentioned.



54

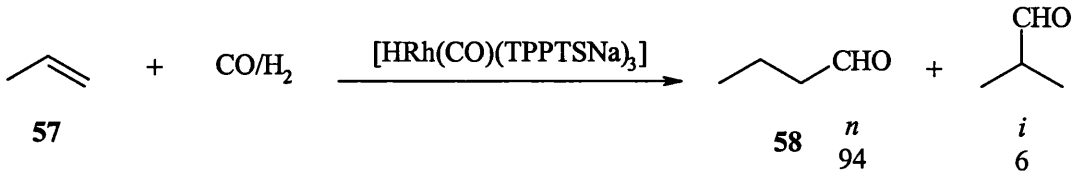
- Figure 7 -

Its new synthesis was reported within the Williams group and it was used effectively in biphasic palladium catalysed Heck reaction.[59] Genet *et al* and Bhanage *et al* have previously reported the uses of TPPDS or TPPTS in the Heck reaction.[60,61] TPPMS has been used not only in biaryl coupling in the Suzuki reaction, but also in a few industrial processes such as hydrogenation, hydroformylation or hydrodimerisation using palladium or rhodium homogeneous catalysts. The Kuraray process is a good example.[48,62,63] It has two major steps with biphasic systems, both using TPPMS **50** with different metal centres for the production of 1,9-nonanediol **56** by first a hydrodimerisation of 1,3-butadiene **55**, Scheme 8.



- Scheme 8 -

The lower solubility of TPPMS in water (80 g/L) ensured TPPTS as the major water-soluble ligand. Many transition metal water-soluble complexes containing TPPTS as ligands have given a wide range of major applications in industry. For example the hydroformylation of propene **57** developed by Ruhrchemie / Rhône Poulenc to produce butyraldehyde **58** is one of the major biphasic industrial successes. It is based on the rhodium complex [HRh(CO)(TPPTSNa)$_3$], Scheme 9.[56] Today more than 300,000 tons of butyraldehyde are produced per annun.

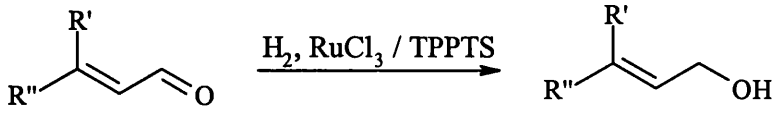


57 **58** *n* 94 *i* 6

- Scheme 9 -

The constant need to improve existing processes is a vital necessity in industry. Therefore the replacement of TPPTS with more efficient water-soluble ligands has been investigated. Ligands such as NORBOS **45**,[31] or BINAS **49** have been developed and their activity compared with TPPTS for the hydroformylation of propene.[64] Activity and selectivity were noticeably increased when BINAS was used and even greater results were reported with the NORBOS ligand.

The hydrogenation reaction of α,β-unsaturated aldehydes **59** to give unsaturated alcohol **60** is another successful example of the application of water-soluble complexes with TPPTS as ligand, Scheme 10.[65]



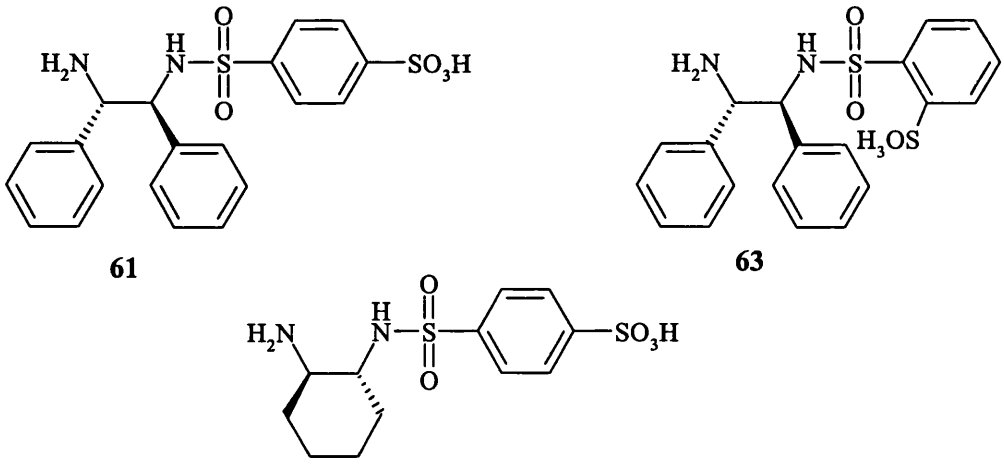
59 60

- Scheme 10 -

- Other sulfonated phosphines

Other sulfonated phosphines such as **48, 52, 53** can also be prepared from a direct sulfonation with oleum.[51] The water-soluble analogue of dppe, **48** has been used with a rhodium complex for the hydroformylation reaction, however it did not show very good activity.[66]

The development and synthesis of three water-soluble analogues of Noyori's and Knochel's chiral ligands have been reported within the group, Figure 8.[67]

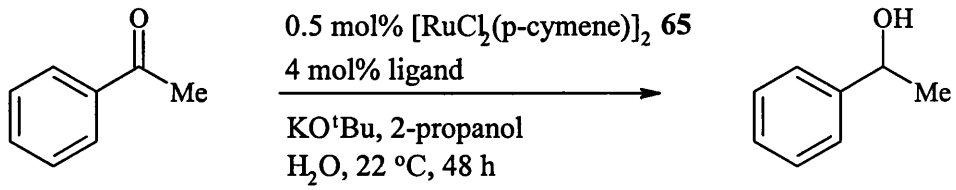


61 63 62

- Figure 8 -

The corresponding enantiomerically pure catalysts formed from these water-soluble ligands and $[RuCl_2(p\text{-cymene})]_2$ **65** have been examined for the reduction of various

prochiral aromatic ketones under transfer hydrogenation conditions. High enantioselectivity and moderate activity were observed in the 2-propanol / base system. An example is shown for the reduction of acetophenone **64**, Table 6.



64

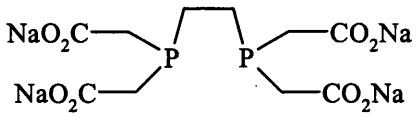
Ligand	Conversion (%)	ee (%)	Alcohol's Configuration
61	96	94	S
62	91	88	R
63	11	91	S

-Table 6 -

Also, ligands **61** and **62** were used with rhodium and iridium complexes to catalyse efficiently the asymmetric reduction of various ketones using the same system 2-propanol / base as previously described, but with up to 51% of water content.[68]

Carboxylated phosphine ligands

Among all the possible water-soluble moieties, the carboxylic group was the first one to be used to obtain water-soluble phosphine ligands. The first examples, such as compound **51**, were reported in the 1950's.[69] The most important of these ligands is the phosphine analogue of ethylenediaminetetraacetic acid (H_4EDTA). It is available as an air-stable monohydrate of the tetrasodium salt, Figure 9.[70]



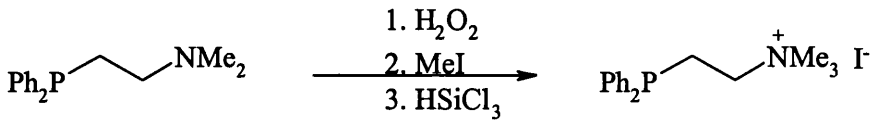
51

- Figure 9 -

More details about the catalytic uses under biphasic conditions of these types of ligands can be found in a short review by Jegorov *et al*, which illustrates the rhodium-catalysed hydrogenation of olefins.[71]

Ammonium phosphine ligands

Phosphines with quaternised aminoalkyl and aminoaryl groups are also good water-soluble phosphines. However, their synthesis requires the protection of the phosphorus centre by either oxidation or coordination to a metal, prior to the alkylation of the nitrogen. The synthesis of the main ligand Amphos **47** is illustrated in Scheme 11. Rhodium complexes of this ligand have been developed for hydrogenation and hydroformylation of alkenes in water or aqueous two-phase system.[72,73]



47

- Scheme 11 -

Other classes of water-soluble ligands containing hydrophilic groups such as 'sugar derivatives' will be discussed later in this chapter.

Although an important number of successful examples of biphasic systems exist, this method can be dependant on the solubility of reagents in the aqueous phase, which then reduce the surface of contact. Also, unlike the homogeneous catalysis, the accessibility and orientation of the substrates towards the catalyst is variable, and therefore the rate and equilibrium position of a certain reaction may well be altered.[74]

2.1.4 Heterogeneous catalysis

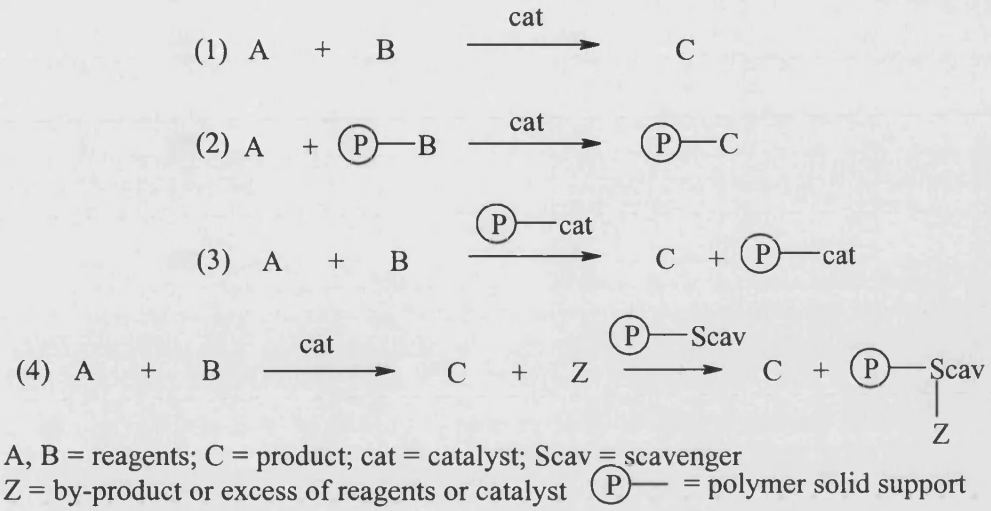
2.1.4.1 Introduction[75,76]

As previously noted, the great advantages of heterogeneous catalysis over homogeneous catalysis are its robustness, long life and especially the ease of separation of the products from the reaction mixture. In order to produce such a catalyst, the immobilisation of catalytically active species onto solid supports has been to a large extent studied over the last decades. In principle, immobilisation can be realised by several methods such as binding of a metal complex onto a solid support, entrapment of metal complexes via in situ synthesis within zeolites or dissolution of a metal complex in a non-volatile solvent that is adsorbed onto the surface of a support. The solid support should also be inert to the reaction mixture and should have a good surface area. Typical examples for organic supports are polymers such as polystyrene or polyamides. Among acceptable inorganic supports are microporous metal oxides such as silica, alumina, zeolites or clays. But the most widely spread solid supports used in organic synthesis are undoubtedly polymers and silica solid supports.

2.1.4.2 Solid phase synthesis

2.1.4.2.1 Organic solid support

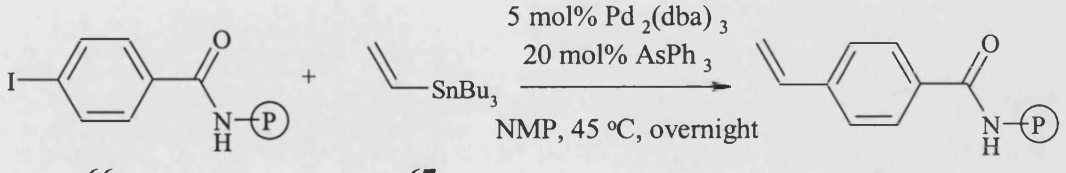
The huge current interest in solid phase organic synthesis can largely be attributed to the development of combinatorial chemistry. Polymer supports are mainly used in this chemistry since the pioneering work of Merrifield in peptide synthesis.[77] In addition since the increasing availability of automated synthesis equipment, combinatorial chemistry has become an important tool in the pharmaceutical industry; indeed it allows the fast synthesis of large numbers of molecules referred to as a library. The use of polymer supports is continuously providing an attractive and practical method for the clean and efficient preparation of novel chemical libraries with potential applications in the pharmaceutical or agrochemical industries. Several reviews dealing with this subject have been reported.[78-81] An outline of how polymeric supports are used is represented in Scheme 12. The equation (1) describes a typical homogeneous catalysis where reagents A and B react in the presence of a catalyst to give compound C. Either a reagent or the catalyst can be directly attached to these solid supports. For example in equation (2) the reagent B is attached to the polymer solid support and then reacts with A to give the supported product. In Equation (3) the catalyst is attached to the solid support and reacts with A and B to give C, and the catalyst is easily separated by filtration from the product C. Polymer supported scavengers will only be mentioned briefly, as they either quench or remove excess reagents, catalysts or by-products, and do not participate into the catalytic reaction, as shown in equation (4), Scheme 12.



- Scheme 12 -

Another key advantage of using solid supported reagents is that it is possible to use excess of the reagent (that is not supported) to drive a reaction to completion, and the separation is effected by simple filtration and rinse of the solid support.

Solid phase synthesis has been applied to a wide variety of organic reactions. Most of these reactions use a solid support where one reagent is linked to a polymer resin. Recently, the application of solid phase synthesis to organometallic reactions such as Heck, Stille or Suzuki has also been reported.[82] An example is the Stille coupling between 4-iodobenzoic acid immobilised as the amide **66** with the vinylstannane **67** in the presence of a palladium catalyst, Scheme 13.[83]

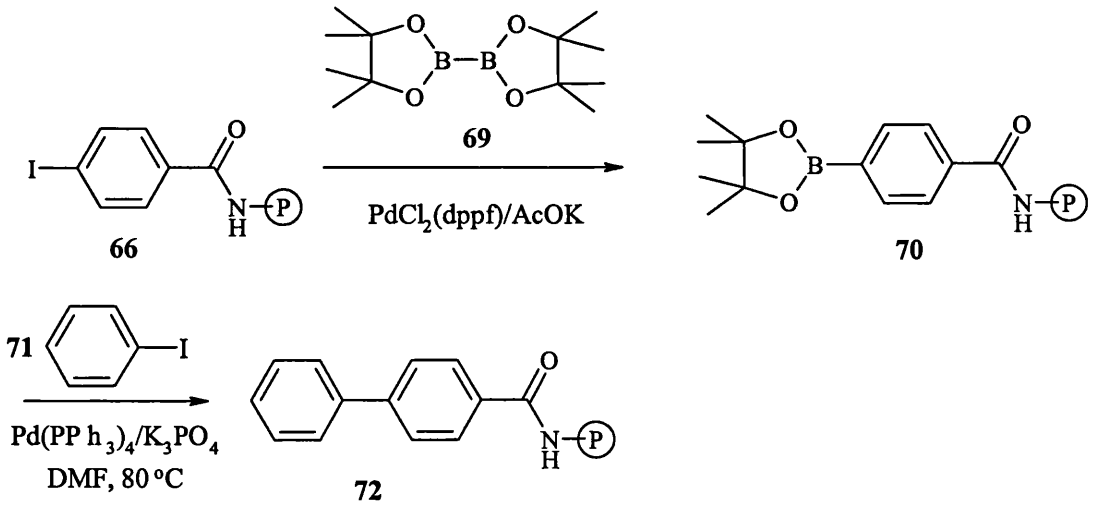


66 **67** **68**

89%

- Scheme 13 -

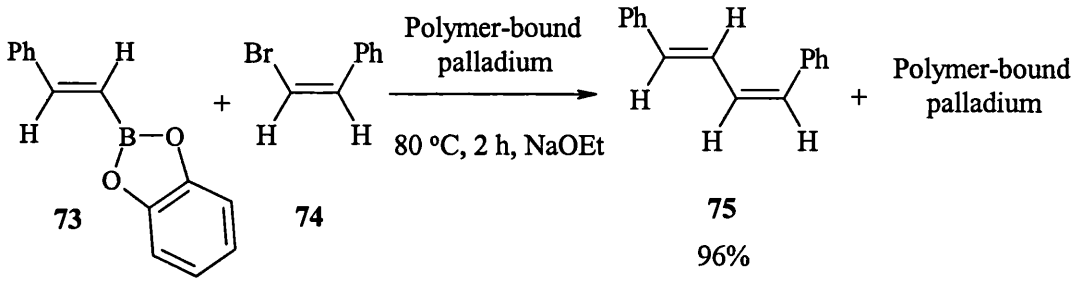
The product was formed in good yield, based on the loading of 4-iodobenzoic acid on the resin and after cleavage from the resin with TFA / DCM. There are also various examples of polymer supported synthesis that have been reported for the Suzuki cross coupling. Attempts to support boronic acids onto solid phase using methodology inspired from peptide synthesis have been achieved with little success. Only recently, Piettre *et al* have reported a procedure involving the use of pinacol ester of diboron **69**,[84] which in the presence of $PdCl_2(dppf)$ and AcOK gave the supported boronate **70** after 20 hours.[85] Under the general conditions of the Suzuki reaction, the boronate **70** reacts with iodobenzene **71** to give the product **72** in good yield (95%) Scheme 14.



- Scheme 14 -

Also, microwave-assisted palladium-catalysed Suzuki couplings for solid phase reaction have been reported to enhance the reaction rates. The coupling of 4-iodobenzoic acid anchored to a resin (TentaGel SRAM), with fluorobenzene boronic acid, provided the corresponding coupling product after only 3.8 min in good yield (99%), after cleavage.[86]

Another possibility for solid phase synthesis is to attach the catalyst to the solid support. A few attempts have been made to realise this approach for Suzuki coupling. One example describes under mild conditions, the polymer-bound palladium catalysed cross coupling of organohalides or triflates with organoboron compounds. For instance, the reaction of the boronic acid **73** with the organohalide **74** in the presence of the polymer-bound palladium catalyst (1 mol%) and sodium ethoxide afforded the coupled product **75** in 96% yield after two hours at 80 °C, Scheme 15.[87]

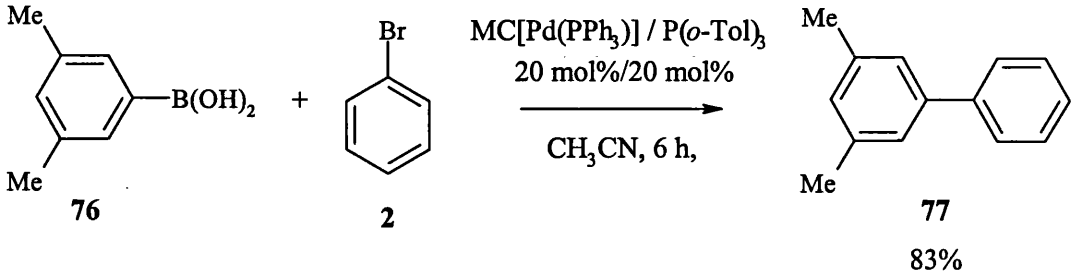


- Scheme 15 -

The supported catalyst, which was prepared from $PdCl_2$ with PPh_3 as added ligand was then separated easily from the reaction mixture and could be reused more than ten times without any decrease in activity.

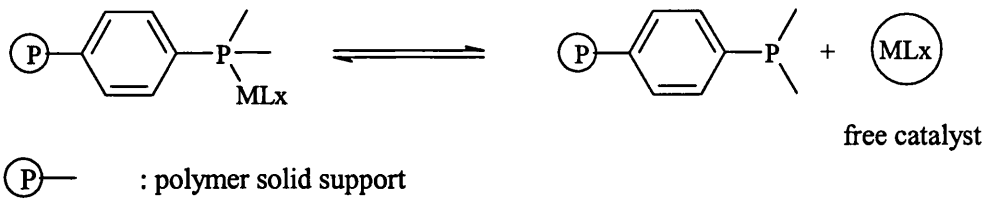
Akiyama and Kabayashi have also reported another interesting example, where the method for the immobilisation of the catalyst is based on physical envelopment by the polymer and on electronic interaction between the π electrons of the benzene rings of the polystyrene-based polymer and the vacant orbitals of the catalyst.[88] They describe this technique as microencapsulated palladium catalyst. The preparation of this catalyst from a mixture of polystyrene and $Pd(PPh_3)_4$ showed in fact that only one triphenylphosphine was remaining on the solid support and they believe that the active catalyst species is the microencapsulated triphenylphosphine palladium denoted as $MC[Pd(PPh_3)]$, but further

addition of phosphines into the reaction was needed. For instance tri(*o*-tolyl)phosphine was added for the Suzuki coupling, and it proved to be efficient for the coupling of boronic acid **76** with bromobenzene **2** in the presence of MC[Pd(PPh_3)] as shown in Scheme 16. The coupled product **77** was produced in good yield (83%).



- Scheme 16 -

Unfortunately, there is no known polymer supported catalyst of industrial importance. In general, many of these catalysts do not reach the industrial development stage due to the huge catalyst-leaching problem. Indeed, metal leaching remains the central problem and until a satisfactory immobilisation technique is available, this kind of approach is unlikely to be viable on large scale. Leaching normally results from the dissociation of the metal from one of the anchored ligands, Scheme 17.[49] Ligand leaching is also a problem, especially for expensive enantiomerically pure ligands.



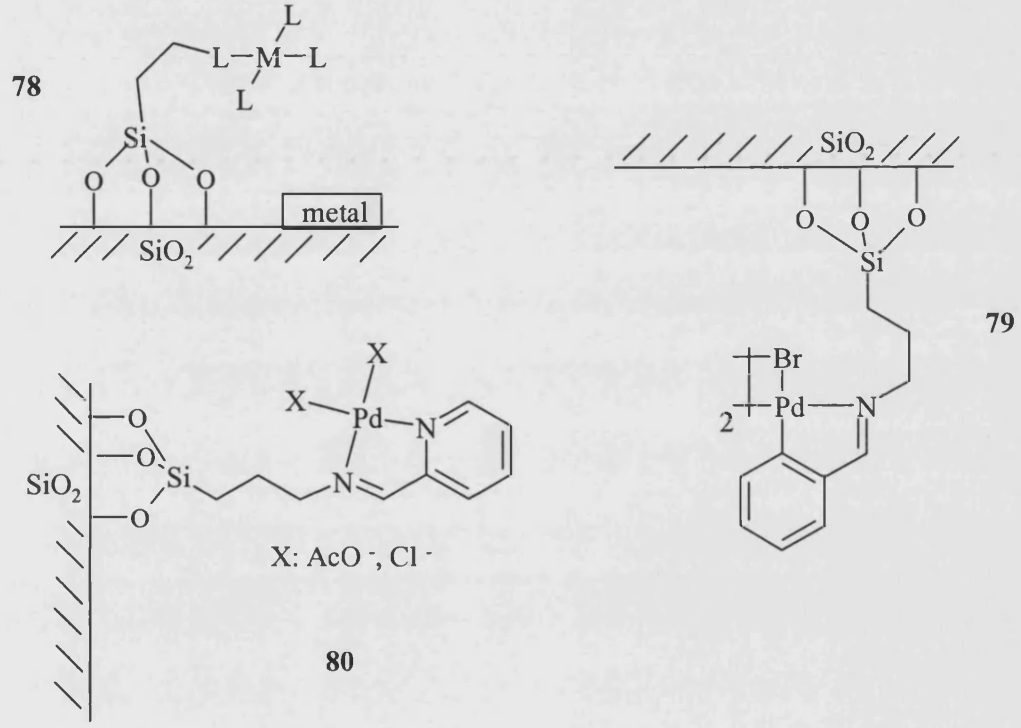
- Scheme 17 -

Because of their much higher thermal and mechanical stability, inorganic solid supports (e.g. silica, alumina) are often preferred over organic polymers for solid phase organic catalysis. Despite the success and advantages of solid phase synthesis using polymer supports, there are also some severe limitations to this approach.[78] Firstly, the reactions can be slower than their solution phase counterparts and the monitoring of reaction progress can be difficult. Besides, additional steps are required to attach and detach products from the resins with more or less success. Finally, the resin loading and swelling characteristics can be poor and many then require the use of solvents that are not necessarily optimal for the reaction being examined.

2.1.4.2.2 Silica solid support

For most inorganic supports, the catalyst is the species preferably chosen to be anchored onto the solid support. This is due to the robustness of these kinds of supports, which then allow the recycling of generally expensive catalysts. Gao *et al* have recently reported an example where a homogeneous catalyst has been tethered to a silica-supported palladium catalyst, **78** (Figure 10).[89] In this original approach, the combination of catalyst consists of a tethered complex on a supported metal (TCSM) catalyst, which could function by synergistic action of both catalyst components. Each component of the catalyst used separately showed lower reactivity for the hydrogenation reaction of various arenes, than the complete catalyst tethered to silica-supported palladium. For example, the complete hydrogenation of toluene at 40 °C, under 1 atm of H_2 in the presence of rhodium isocyanide complexes gave methylcyclohexane with turnover numbers of 2,420 after 8.5 h of reaction, in comparison with 143 for the catalyst only tethered to a silica support, or 0 for the free isocyanide complexes.

Apart from hydrogenation reactions, there are a few examples of anchored catalysts on silica supports, which have been reported for Suzuki reactions. An illustration is the two other catalysts in Figure 10, where the palladium complexes have been attached to a silica support.



- Figure 10 -

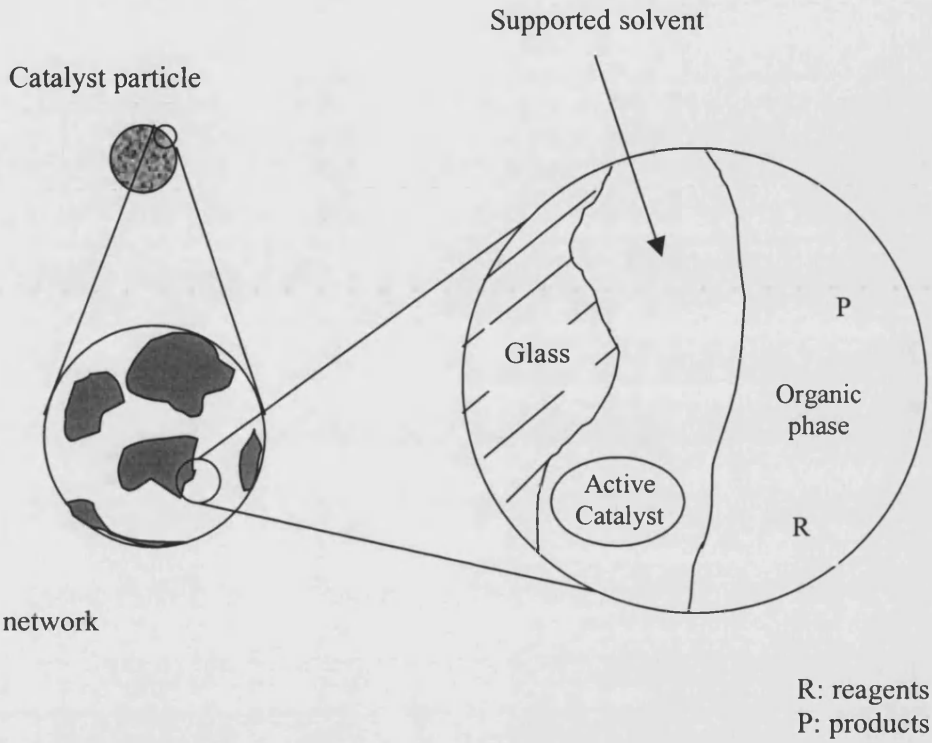
Mubofu *et al* have reported the application of catalyst **80** for the coupling between phenylboronic acids and various aryl bromides, in the presence of K_2CO_3 as base.[90] Catalyst **80** is composed of a diimine-based ligand that is attached to a silica solid support. The reaction proceeded smoothly with high activity and without extra addition of phosphine ligands. In addition, no metal leaching was observed and the catalyst was reused several times. A typical example is the reaction of bromobenzene with phenyl boronic acid that gave the biphenyl after three hours in 98% yield. As previously

described, palladacycles have recently been reported as highly efficient catalysts for palladium catalysed reactions, with enormous turnover numbers. Therefore attempts to transpose these catalysts to heterogeneous catalysts are being investigated. Bedford *et al* have reported silica supported imine-based palladacycle catalysts for Suzuki cross coupling.[91] The imine-based palladacycle was attached to a silica support to form catalyst **79** as shown in Figure 10. The reactivity of the supported catalyst has been tested for the coupling of diverse aryl bromides with phenylboronic acid. But unfortunately, the catalysts not only show considerably lower reactivity than their homogeneous counterparts but also a poor recyclability. Although the catalysts did not give the expected results especially for recycling, their modes of decomposition gave vital information for understanding the mechanism and leaching problem for these highly active imine palladacycle catalysts.

2.1.4.3 Supported aqueous phase catalysis

In general, major immobilisation techniques for heterogeneous catalysis never approach the combined activity and selectivity performance levels of their homogeneous equivalents (due to the limited mobility of the anchored catalyst) and have a tendency to allow leaching of the metal complexes. A solution to this problem has emerged with the development of supported aqueous phase catalysis (SAPC) by Davis *et al.*[47] Indeed such hybrid catalysts are fruitful subjects for research for both academic and industry as they combine the attribute of conventional homogeneous catalysis with the experimental simplicity of heterogeneous catalysis. It appears that the SAPC technique merges advantages from both homogeneous and heterogeneous catalysis, which are respectively the use of defined catalytic species, mild reaction conditions, high activity and easy

separation process. It is seen as an elegant way of heterogenising biphasic catalysts. A schematic diagram of the design of a heterogeneous catalyst is shown in Figure 11.



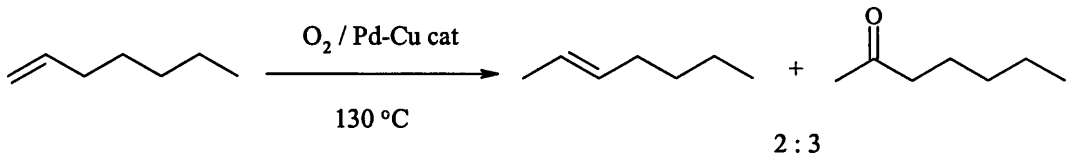
- Figure 11 -

Supported aqueous phase catalysis has been designed especially for liquid-liquid reagents, while supported liquid phase (SLP) catalysis was originally designed for gas phase reactions. As shown in Figure 11, the SAP catalysts consist of a thin film that resides on a high surface area of a hydrophilic support such as controlled-pore glass (CPG) or silica. It is composed of water-soluble organometallic complexes and a supported solvent such as water or ethylene glycol. The originality of this technique is that the metal complex is not attached to the solid, but supported in order to allow its free movement within the supported solvent. The water-soluble complex is supported on a hydrophilic solid to create a large interfacial area between the catalytic species and the organic reagents. The

hydrophilicity of the ligands and the silica creates interactions with sufficient energies to maintain the immobilisation of the complex.

The efficiency of this method has been proven for important industrially relevant examples such as hydroformylation. The rhodium complex $HRh(CO)(TPPTS)_3$, and TPPTS were impregnated onto controlled-pore glass (CPG-240) and used effectively to hydroformylate oleyl alcohol at 100 °C and 49 atm CO + H_2 ($CO:H_2$, 1:1).[92] Further work showed that the rhodium is not leached into the organic phase. Long-term stability of the SAP catalysts is an important issue, therefore Davis *et al* tried to investigate the stability of the rhodium complex $HRh(CO)(TPPTS)_3$. The complex, TPPTS and water were placed into a reactor with cyclohexane and 1-heptene. The mixture was put under 68 atm CO + H_2 ($CO:H_2$, 1:1) and heated with stirring to 100 °C. The second experiment was carried out in the same way, except that CPG-240 was added to the solution. After 14 hours, the conversion into the corresponding aldehyde was almost 70% for the experiment containing CPG-240 and about 5% for the one without the CPG-240. They then demonstrated that under the same conditions, the individual components of the SAP catalyst were more stable assembled as the SAP catalyst configuration than separated. Consequently the leaching or the partition of the solution and the complexes from the support is not likely to happen under the general reaction conditions.[93] Horvath has investigated the influence of the lipophilicity of the reagents towards the SAP catalysts.[94] The results showed that the water solubility of the olefins does not limit the performance of the SAP catalysts, as turnover numbers remained independent of the number of carbon atoms present in the molecule. The SAP catalysts have also been applied to the Wacker process.[95] The catalyst was prepared by adsorbing palladium and copper onto CPG-240 in the presence of water. The substrate 1-heptene was converted to 2-heptene and

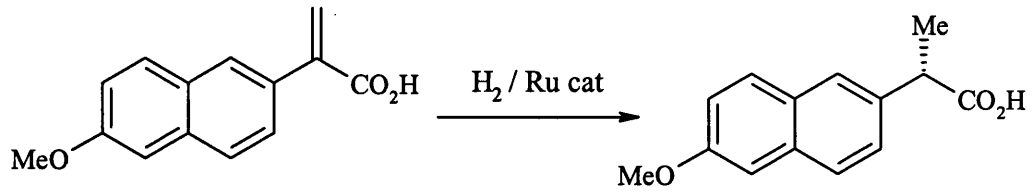
2~heptanone at 4 - 15 atm O_2 and 130 °C. Unfortunately the ratio of isomerisation / oxidation was about 2:3, Scheme 18.



- Scheme 18 -

However, they believe that appropriate modifications to the systems should decrease the rate of isomerisation.

Asymmetric synthesis is an important feature in organic synthesis, especially for organometallic chemistry. More and more the high cost of the transition metal is overcome by the increasing price of highly designed and elaborated chiral ligands. Consequently the availability of a heterogeneous asymmetric catalysis that can be recycled is important. Wan and Davis have used the SAP catalysis for the asymmetric synthesis of Naproxen **85**, by asymmetric hydrogenation of starting material **84**, Scheme 19.[96]

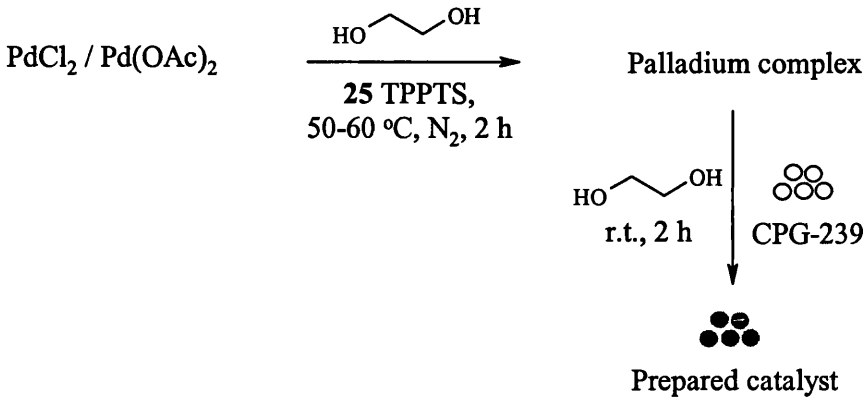


84 **85**

-Scheme 19 -

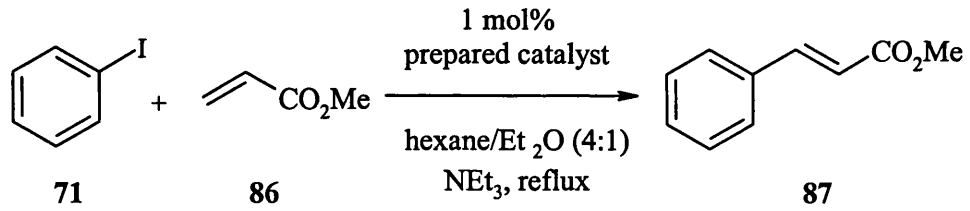
In their initial attempts, they prepared the catalyst with the water soluble ruthenium complex, [Ru(BINAP-4SO_3Na)(benzene)Cl]Cl, where water was the immobilised solvent on the CPG, named a hydrated SAP catalyst.[97] The activity and enantioselectivity of this catalyst were found to be sensitive to the amount of water trapped on the catalyst. The increase of the water content led to a better enantioselectivity and activity. The results were attributed to a better mobility of the ruthenium complex within the support. However, the performance of the SAP catalyst was only moderate and its enantioselectivity was dependent on the enantioselectivity of the separate ruthenium complex, which is low in water. This is mainly due to the cleavage of the ruthenium-chlorine bond by water.[98,99] They found that anhydrous ethylene glycol was a better supporting solvent than water, as it prevented the cleavage of this bond. The new heterogeneous catalyst consisted then of a ruthenium complex dissolved in a film of ethylene glycol, which is supported onto the CPG support.[100] As previously reported for the hydrated SAP catalyst, both the activity and enantioselectivity of this catalyst remained sensitive to the amount of ethylene glycol in the catalytic system.

Palladium catalysed reactions are also an important class of reaction. For example the Heck reaction has attracted much attention for its heterogenisation with various silica supports.[50,101] As the SAP catalysis has demonstrated a great potential, the application of this method, also called Glass Bead Technology, to the Heck reaction has been investigated within the group. The initial efforts focused on the preparation of the glass bead catalyst from either palladium chloride or acetate in the presence of TPPTS **25** or TPPMS **50** and ethylene glycol to give the palladium complex, which was then loaded onto CPG-239 beads with additional ethylene glycol, Scheme 20.



- Scheme 20 -

The prepared catalysts were then examined for their ability to catalyse the Heck reaction between iodobenzene **71** and methyl acrylate **86** in a 4:1 mixture of hexane and diethylether. The results for the synthesis of product **87** are summarised in Table 7.



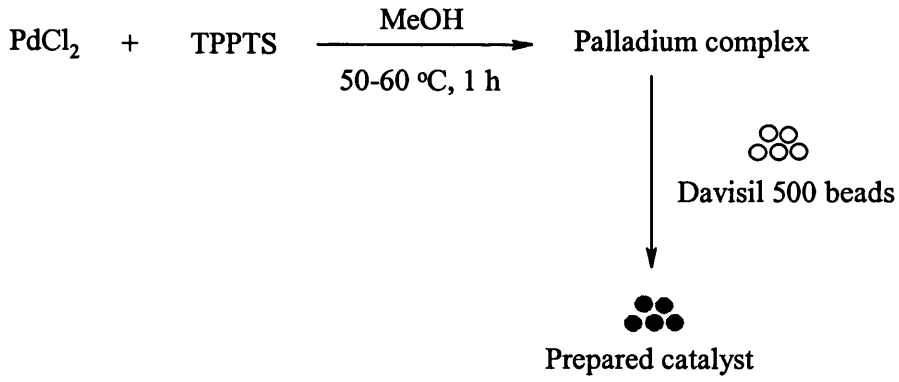
71 **86** **87**

Entry	Beads	Ligand	Catalyst	Time (h)	Yield (%)	Pd leaching (ppm)
1	CPG-239	TPPMS	$Pd(OAc)_2$	25	63	0.5
2	CPG-239	TPPTS	$PdCl_2$	25	75	0.2
3[a]	CPG-239	TPPTS	$PdCl_2$	25	27	0.4
4	CPG-120	TPPMS	$PdCl_2$	23	74[b]	2.5
5	Davisil 300	TPPMS	$PdCl_2$	21	73[b]	2.5

[a] recycling: 4 times, [b] conversion and 5 mol% of prepared catalyst were used.

- Table 7 -

The optimisation of the reaction was realised by investigating the use of different types of glass bead and ligand. TPPTS was found to give less palladium leaching than TPPMS, this result was attributed to the stronger hydrophilic property of the TPPTS palladium complex. Additionally, TPPTS is known to reactivate the catalyst and an excess of ligand stabilises the system against decomposition.[101] The recycling of the catalyst was examined, unfortunately after four reuses the yield dropped to 27% (entry 3 Table 7). This was attributed to the formation of phosphine oxide, which led to a less efficient catalyst. The optimised prepared catalyst with TPPTS as ligand was found to be effective in the Heck coupling of various other products.[102] However for more polar substrates such as acrylic acid, which is normally a good coupling partner, this glass bead catalyst only gave low yields and high palladium leaching. An alternative catalyst was prepared from the complexation of $PdCl_2$ with TPPTS in methanol and addition of Davisil 500 Å. The final catalyst was isolated after removal of the solvent and dried in an oven, Scheme 21.

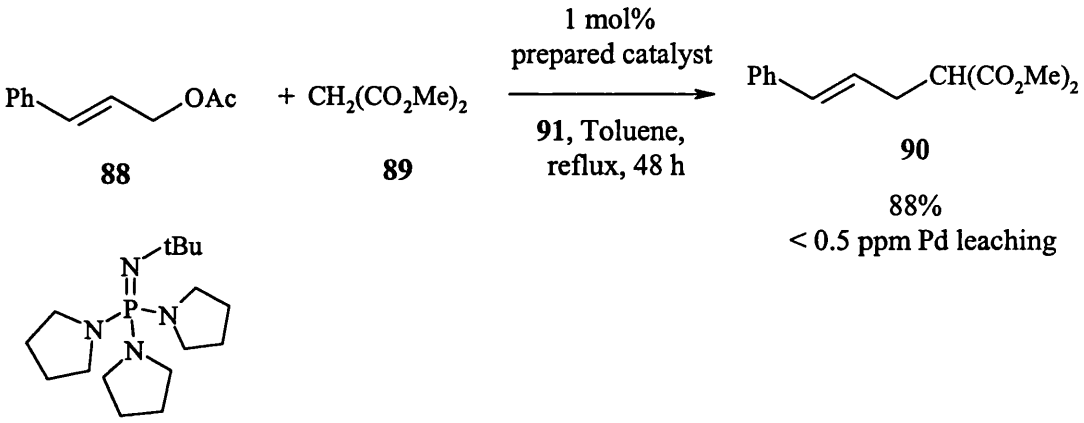


- Scheme 21 -

The new catalyst with minimal solvent and without ethylene glycol was still active for the Heck reaction, but gave slightly higher palladium leaching. For example the typical coupling of iodobenzene **71** and methyl acrylate **86** gave the Heck coupling product **87**

with 71% yield and 2.3 ppm palladium leaching when the ethylene glycol-free beads were used. Also preliminary results have shown that this catalyst is more efficient for the coupling of polar substrates.

The palladium catalysed allylic substitution was also examined using the glass bead technology.[102-104] The preparation of the catalyst includes the use of TPPTS as the water soluble ligand and $Pd(OAc)_2$ as the palladium source and ethylene glycol was also used. Finally, the bulky base phosphazene **91** was chosen as it preferably resides in the bulk organic layer. A typical example is shown below in Scheme 22.

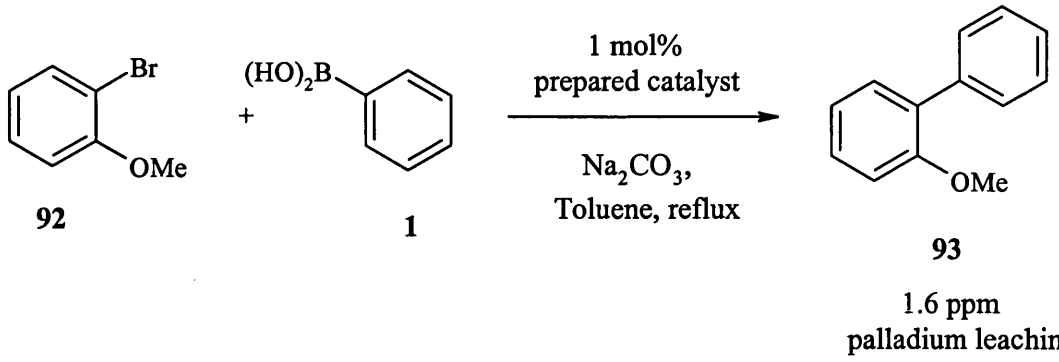


91 phosphazene base

- Scheme 22 -

The allyl acetate **88** and malonate **89** reacted successfully in the presence of the catalyst to give the corresponding allylic substitution product **90** in good yield (88%) and with a low level of palladium leaching (< 0.5 ppm).

The Suzuki cross coupling is another example of possible application of the glass bead technology developed within the group. Only a few attempts have been tried to show the efficiency of the catalyst.[105] The aryl bromide **92** was coupled to phenylboronic acid **1**, in the presence of 1 mol% of the prepared catalyst, and Na_2CO_3 as base, Scheme 23.



- Scheme 23 -

The corresponding biphenyl product **93** was isolated in good yield (95%) after 7 hours. Although an aqueous base was used in the reaction, a moderate palladium leaching of 1.6 ppm was observed. The presence of water did not increase the leaching dramatically.

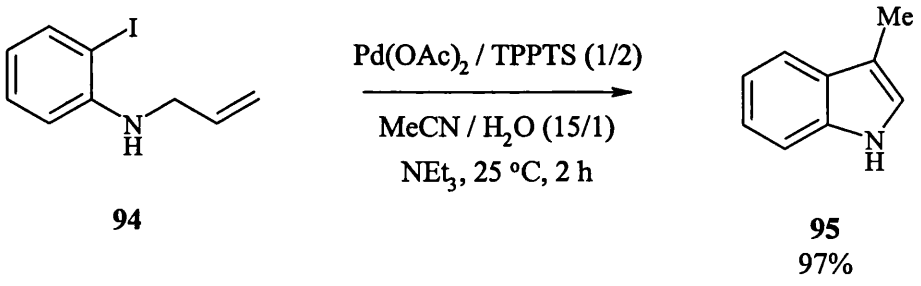
2.1.5 Conclusion

The conversion of well established homogeneous catalysts into heterogeneous systems has been widely studied to try to overcome the costly and time-consuming problems of separating products from catalysts. In addition there is a constant need, especially in the pharmaceutical industry, to reduce metal leaching and anchoring the catalyst onto a solid support is one possible solution. In the last few decades the development of techniques such as solid phase catalysis using organic or inorganic solid supports, where either reagents or catalysts are attached to a solid support gave interesting results. In most cases an easy separation was observed, however due to the restricted mobility of the attached catalyst, for most of these techniques problems such as metal leaching and particularly lower activity and selectivity than the homogeneous counterpart are observed. On the other hand the SAP catalyst is a hybrid system combining advantages from both heterogeneous catalysis and biphasic systems where a water-soluble catalyst is free within

a hydrophilic supported solvent around the glass beads. This new approach has shown high activity and has proven to be a good asymmetric catalyst. The results observed within the group for reactions such as Heck or allylic substitution have proven that this technique holds potential for palladium-catalysed reactions.

2.2 Suzuki Cross Coupling in Aqueous Media

Throughout the past three decades, the development of diverse water-soluble ligands for organometallic catalysts was mainly due to the emergence of biphasic reactions, with all its practical advantages as reported in the previous sections. In academic laboratories the sulfonated phosphine ligands have mainly been used for palladium-catalysed reactions such as Heck, Stille, Sonogashira or Suzuki processes.[106] For example, the intramolecular Heck coupling of *o*-iodo-*N*-allylaminobenzene **94** in the presence of $Pd(OAc)_2$/TPPTS under mild conditions has been examined. The cyclised product **95** was then produced after two hours in high yield 97%, Scheme 24.



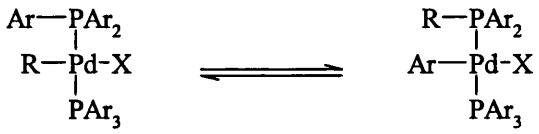
94

95
97%

- Scheme 24 -

The Suzuki cross coupling is a powerful and versatile tool in organic synthesis and in this case the reaction already tolerates aqueous conditions due to the general use of mineral bases. Consequently, much attention has been given to get the Suzuki reaction to work

effectively in water or aqueous media, especially with the economy and safety of using water as solvent in industry. "Ligandless" palladium acetate catalysed Suzuki cross coupling reaction of aryl bromides with aryl- and vinylboronic acids in water, with or without the presence of tetrabutylammonium bromide, has been reported to give high yields and to accelerate considerably the rate of the coupling.[107-110] Such catalysts containing no phosphine ligands are advantageous as they eliminate the side reaction, in which there is an interchange between the phosphorus-bound aryl moieties and palladium-bound aryl or alkyl groups, as shown in Scheme 25. Consequently in the rest of the catalytic cycle the aryl group from the ligand takes the place of the R- group from the organohalide, generating an undesired by-product.

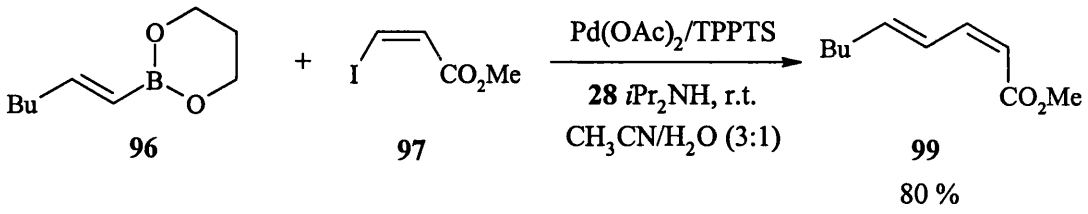


- Scheme 25 -

Although the side-reaction is avoided, the complete conversion of the coupling is not always possible under these conditions, particularly for slow reactions with electron-rich and / or sterically hindered organohalides.

Savignac *et al* have been engaged in the last decade in the study of the water soluble catalyst Pd(II)/TPPTS to deprotect functional groups such as alcohol, in Heck reaction, but especially for the Suzuki cross coupling in aqueous media.[106] The optimisation of the Pd(II)/TPPTS catalyst led to the fact that the palladium source $Pd(OAc)_2$ or $PdCl_2$ does not influence the efficiency of the catalyst. Also the optimal ratio observed for $Pd(OAc)_2$/TPPTS was 1:3, where one equivalent of the ligand reduces Pd(II) to Pd(0) and

the remaining two equivalents stabilise the Pd(0).[111] Finally diisopropylamine **98** was found to be a more effective base than inorganic bases such as K_2CO_3 or $Ba(OH)_2$. An example is described in Scheme 26, where the coupling product **99** was isolated in good yield.

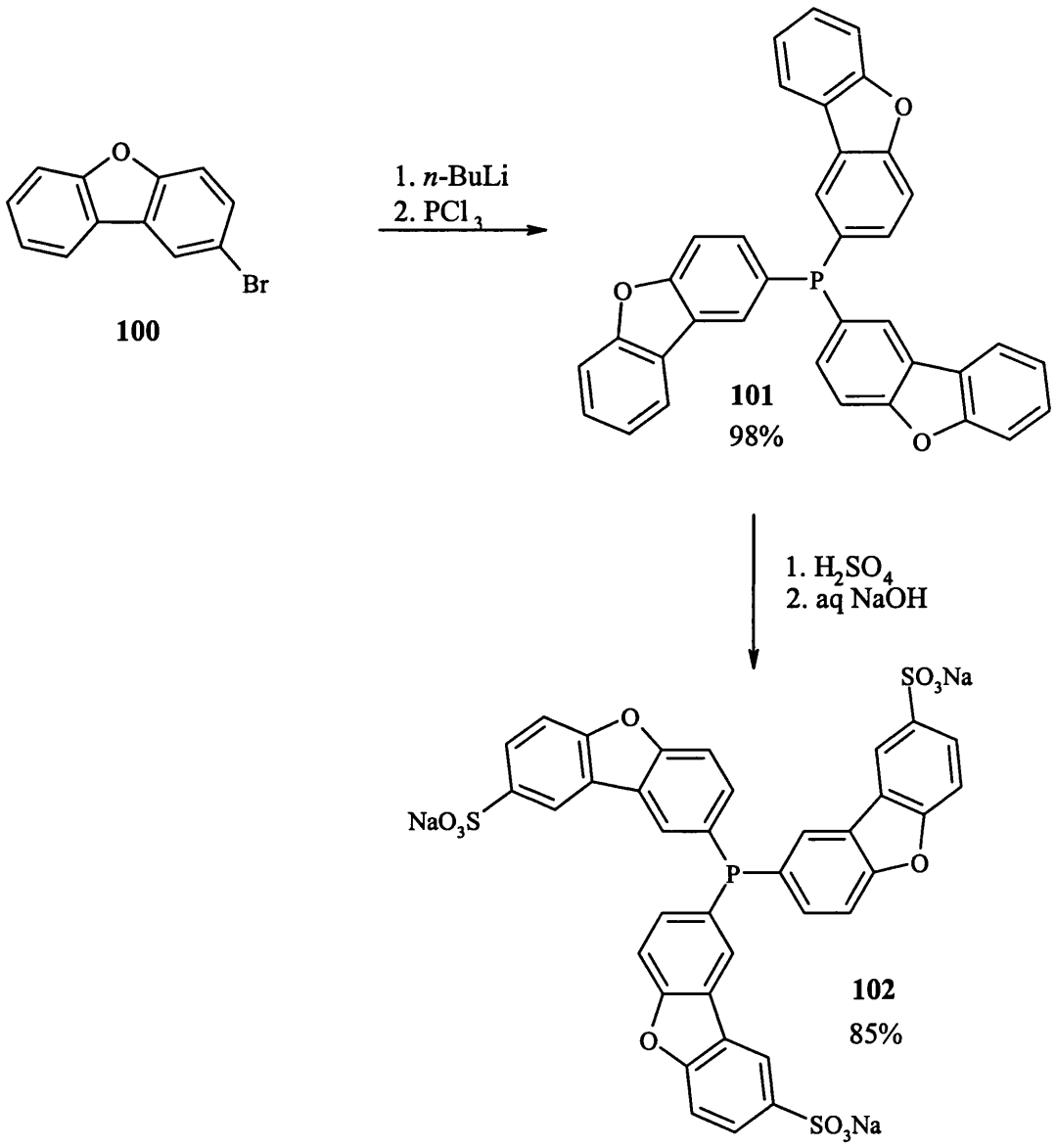


- Scheme 26 -

More recently, the same catalytic system was reported to show high activity and turnover numbers for the Suzuki reaction of various aryl bromides with boronic acids. In addition the recycling of the catalyst was achieved three times without loss of activity.[112] Also, Casanuovo and Calabrese have reported the use of the ligand TPPMS with for instance Na_2PdCl_4 as the palladium source for the coupling of various organohalides and arylboronic acids in aqueous media or water. The coupled products were produced with moderate to excellent yields (47% to 98%).[113]

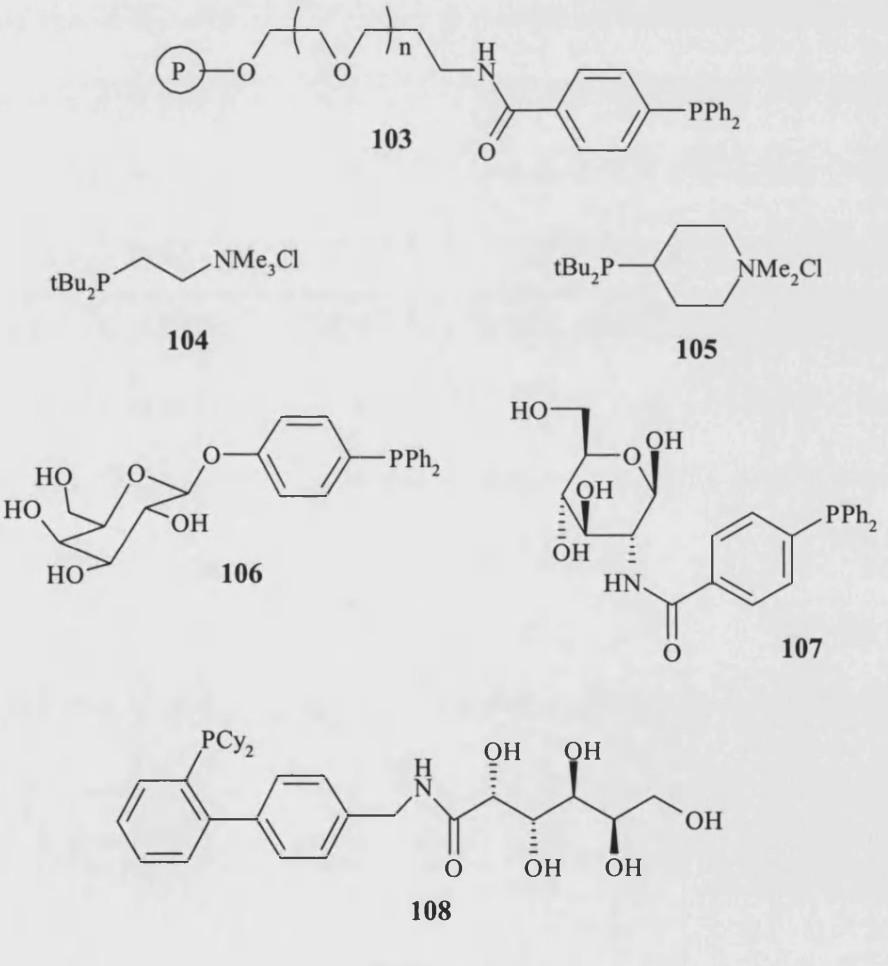
New sulfonated water-soluble ligands based on a dibenzofuran moiety have been reported by Hiemstra *et al.* [114] The synthesis of the dibenzofuran based mono-, di- and tri-sulfonated ligands was achieved in two steps in good yields and without formation of phosphine oxides. The typical procedure is presented for the synthesis of the tri-sulfonated ligand **102**, Scheme 27. The solubility of this ligand in water is more than 1000 g/L and is about 800 g/L for the corresponding disulfonated ligand. The water-soluble catalyst was prepared from ligand **102** and $Pd(OAc)_2$ in a ratio of 1:3, and showed good activity in the presence of NEt_3 for the Heck reaction and Na_2CO_3 for the Suzuki cross

coupling. For example the Suzuki reaction of 4-methyl iodobenzene with phenylboronic acid in a mixture of H_2O/MeCN (1:2) gave the corresponding coupled product in good yield 90%.



- Scheme 27 -

So far, most water-soluble phosphines used for the Suzuki cross coupling have ionic groups such as sulfonate group $-SO_3M$ or quaternary ammonium salts $-NR_3X$ as shown in Figure 12. Ligands **104** and **105** were particularly designed for the cross coupling of chloroarenes as they show a strong electron donating ability towards the metal centre.[115] However a new class of polar hydrophilic triarylphosphines for two-phase or mono aqueous catalysis has been developed. They contain neutral polar groups and the hydrophilicity of these new ligands is attributed to the sugar derivative moiety. A few examples of these carbohydrate-based phosphines are also shown in Figure 12.

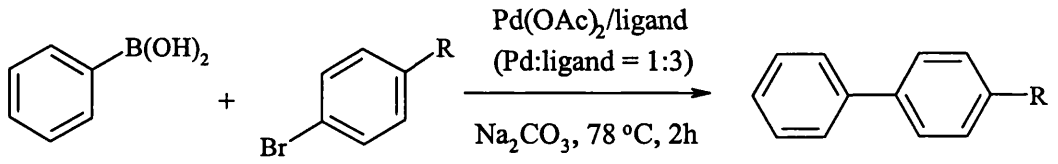


- Figure 12 -

Although the polymer supported ligand **103** does not have any sugar moiety, it is has been reported that such polymer resins based on a polyethylene glycol-polystyrene graft co-polymer (PEG-PS) display good swelling properties in organic solvents but also in water.[116,117] The use of this type of polymer was first examined as an amphiphilic resin to prepare polymer-supported palladium phosphine complexes for allylic substitution.[118,119] The resin-supported palladium phosphine complexes prepared with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ have also been reported to catalyse the Suzuki cross coupling of various arylhalides with arylboronic acids in water.[120]

The structure of ligand **108** was inspired by the 2-(dicyclohexylphosphino)biphenyl ligand designed by Buchwald.[14,27,121] A sugar side chain was introduced to convert the original ligand into a water soluble one.[122] The combination of ligand **108** with $Pd(OAc)_2$ gave a catalyst used in water, that showed high activity in the cross coupling reaction of various bromo or iodoaryl substrates. For example the Suzuki reaction between 4~bromoacetophenone and *p*-tolylboronic acid in the presence of 0.001 mol% of catalyst gave the product in high yield and with a turnover number of 96,000. Also the $Pd(OAc)_2$/**108** catalyst has provided similar efficiency for the cross coupling of various chloroarenes.

The two other ligands **106** and **107** have similar structures. The catalyst prepared from ligand **106** and $Pd(OAc)_2$ was reported by Beller and co-workers to catalyse the coupling of phenylboronic acid with several bromoaryl compounds and it was compared to $Pd(OAc)_2$/TPPTS, Table 8.[123]



1

R	Ligand	Yield (%)	TON
COMe	**106**	90	9,000
COMe	TPPTS	87	8,700
Cl	**106**	71	7,100
Cl	TPPTS	44	4,400

- Table 8 -

The $Pd(OAc)_2$/**106** gave the coupled products in high yields (90% for the coupling of 4~bromoacetophenone and 71% for 4-bromochlorobenzene) and higher turnover numbers than TPPTS especially for the chloroaryl.

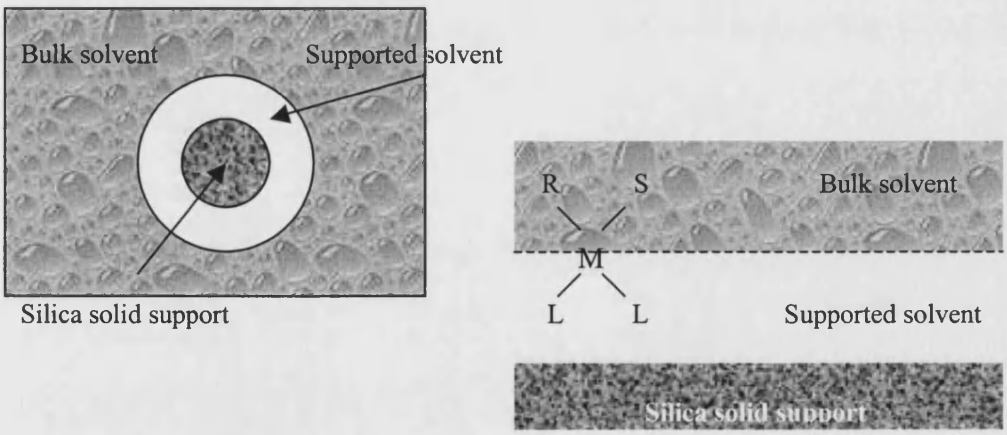
Sinou *et al* have reported the synthesis of ligand **107**, and the use of the water-soluble catalyst $Pd(OAc)_2$/**107** in Suzuki cross coupling. The efficiency of the catalyst proved to be high and it was recycled three times without loss of activity.[124]

In summary, the use of carbohydrate derivatives as ligands for palladium cross coupling in aqueous media or water is only at the beginning. In general, all these new ligands have shown higher activity and also higher turnover numbers than their famous TPPTS or TPPMS counterparts.

2.3 Results and Discussion

2.3.1 Aims of the project

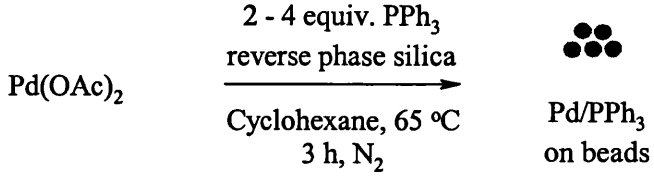
The objective of the project is to apply the glass bead technology to the Suzuki cross coupling reaction. This reaction is an important synthetic tool in organic chemistry and the design of a recyclable heterogeneous catalyst is a challenge, particularly for industry. The supported aqueous phase catalysis or the glass bead technology has been applied with success to various catalysed reactions within the group, as previously described. But another version of this technique using a reverse phase catalyst for the Heck reaction and for enantioselective substitution reactions has also been reported within the group.[125] This new catalyst involves the derivatisating the hydrophilic surface of a silica support, glass bead, with a long lipophilic chain such as octyltrimethoxysilane, using known methods.[126] A thin hydrophobic layer then resides all around the bead and the reaction is believed to occur at the phase interface, as described in Figure 13. The polar product remains in the aqueous phase.



R: Reactant, S: Substrate, L: Ligand, M: Metal

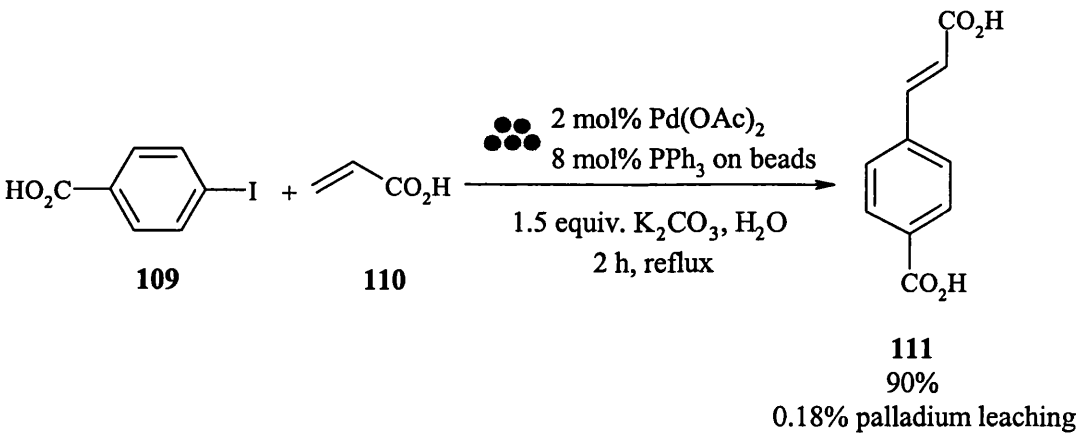
- Figure 13 -

The great advantage of this catalyst is that instead of having a hydrophilic supported solvent with polar complexes around the silica solid support, a standard organic catalyst can be used and the reaction can proceed either in water or with a polar solvent with water as co-solvent. This holds many environmental benefits, which may be especially important for industry. The catalyst was prepared from $Pd(OAc)_2$ and triphenylphosphine as shown in Scheme 28.



- Scheme 28 -

An example of the efficiency of the reverse phase catalyst is demonstrated for the Heck coupling between iodobenzoic acid **109** with acrylic acid **110** in water and at reflux, as described in Scheme 29. The coupled product **111** was isolated in good yield (90%) and with a low level of palladium leaching (0.18%), Scheme 29.



109 **110**

111
90%
0.18% palladium leaching

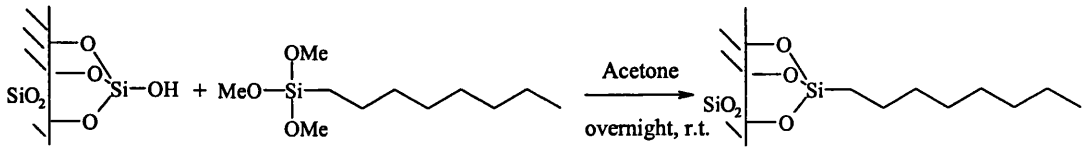
- Scheme 29 -

During this project the preparation of the reverse phase catalyst would be first optimised with the conventional catalyst $Pd(PPh_3)_4$, which is commercially available and also easy to synthesise. Davisil 500 Å was chosen as the silica solid support for all of this study. The prepared glass bead catalyst will then be tested for the Suzuki cross coupling of various reagents in water. The recycling of the reverse phase catalyst and the palladium leaching in the final products will then be investigated. Then various studies will be undertaken to understand in further details the scope and limitation of this technique applied to the Suzuki cross coupling.

2.3.2 Reverse phase catalysis

2.3.2.1 Preparation of the catalyst

The first step is to derivatise the surface of the glass beads (Davisil 500 Å) at room temperature in acetone using an excess of octyltrimethoxysilane **112**, as shown in Scheme 30. The long octyl side chains attached to the silica solid support create a lipophilic layer around the beads. After stirring overnight the reverse phase silica is then collected as a white powder after drying under high vacuum.



Davisil 500 Å **112**

- Scheme 30 -

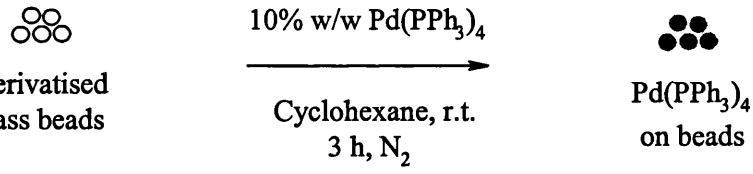
The derivatised glass beads are then converted into an active supported catalyst using tetrakis(triphenylphosphine) palladium as the catalyst.[125] A loading of 10% w/w of the catalyst was chosen. When $Pd(PPh_3)_4$ was not purchased, it was synthesised from

palladium dichloride and triphenylphosphine following a general procedure reported in the literature, Scheme 31.[127]

$$PdCl_2 + PPh_3 \xrightarrow[DMSO,\ N_2,\ heat]{NH_2NH_2} Pd(PPh_3)_4$$

- Scheme 31 -

Scheme 32 illustrates the general conditions for the conversion of the reverse phase glass bead into the active catalyst. $Pd(PPh_3)_4$ is loaded onto the derivatised glass bead by stirring overnight the catalyst into a mixture of cyclohexane and the derivatised glass beads under nitrogen. After removal of excess solvent, the supported catalyst can be handled under a normal atmosphere. It is assumed that the catalyst is still mobile within a thin film of cyclohexane on the surface of the glass bead and that reaction occurs at the solvent interface.

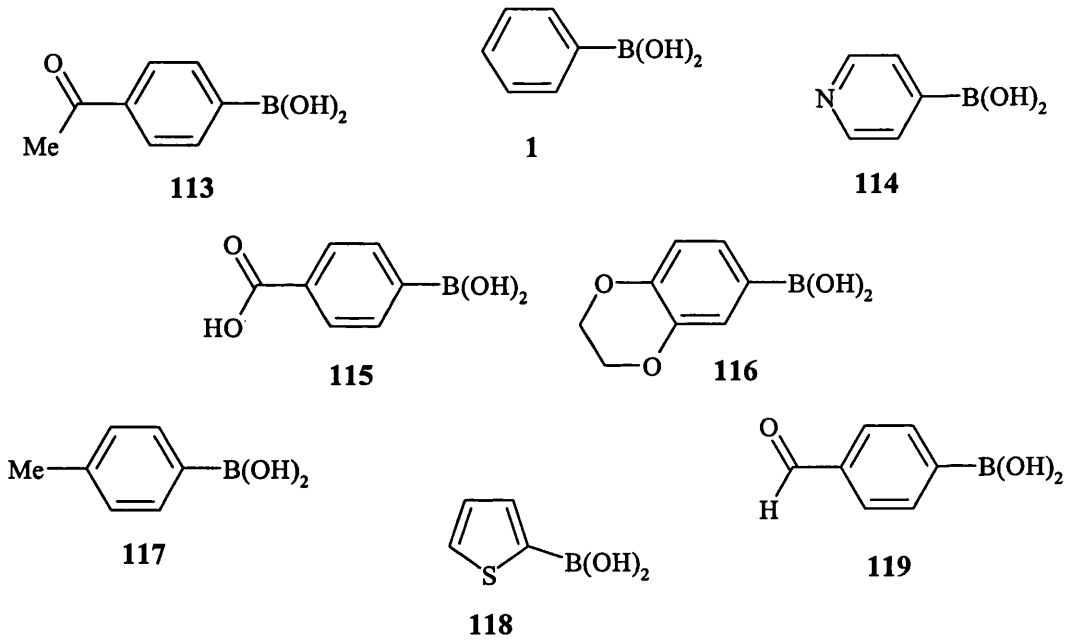


- Scheme 32 -

The reactivity of $Pd(PPh_3)_4$ on beads which is called the reverse phase catalyst has then been investigated for the Suzuki cross coupling in water of various aryl halides and boronic acids.

2.3.2.2 Reactivity of the catalyst

The efficiency of the reverse phase catalyst has been examined for the cross coupling of several boronic acids, as represented in Figure 14. The inorganic base Na_2CO_3 was used for most of the reactions investigated and the reaction was heated at reflux until completion of the reaction. Since the reactions have been realised in a single aqueous phase, most organohalides reagents and boronic acid **115**, which have polar functional groups such as a carboxylic acid substituent were solubilised by the addition of an extra equivalent of base.



- Figure 14 -

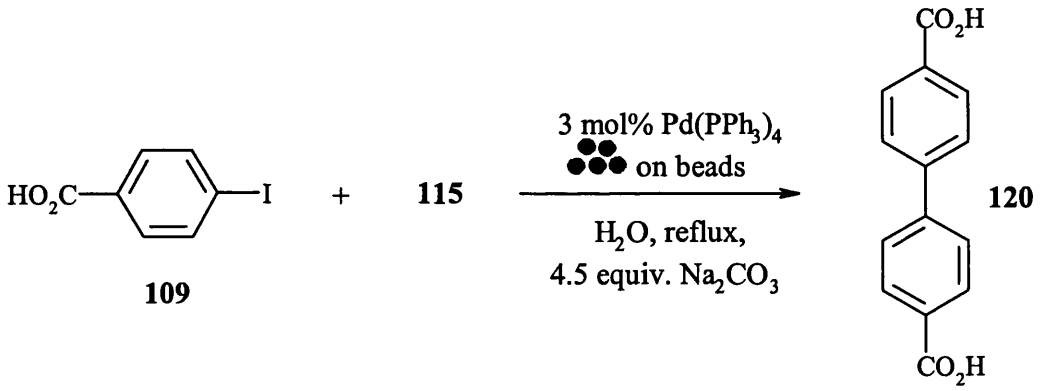
Although the other boronic acids other than **115** are less water soluble, their coupling in the presence of the reverse phase glass beads has been investigated exclusively in water, except for boronic acid **114** where a mixture of acetonitrile and water has been found to be more efficient.

- *4-carboxylic phenyl boronic acid, 115*

The cross coupling of boronic acid **115** with iodo- and bromoaryls has been investigated. The cross coupling reaction with iodoalkenyl compounds and the formation of self-coupling products will also be discussed.

*** Cross coupling with iodocompounds*

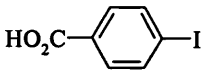
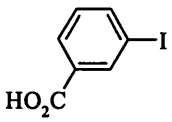
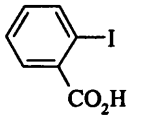
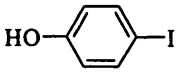
In a typical Suzuki reaction, boronic acid **115** has been coupled with 4-iodobenzoic acid **109**. The reaction was carried out in water in the presence of 3 mol% of the reverse phase catalyst and 4.5 equivalents of base, Scheme 33. After only five minutes, the coupled product **120** was synthesised in good yield (86%) and a minimal palladium leaching of 0.06% was found in the product, entry 1 of Table 9.



- Scheme 33 -

The synthesis of compound **120** was confirmed by the ^1H NMR that displays a single pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the benzene ring and which is identical to the commercial product. The chemical ionisation mass spectrum exhibits an ion m/z 242.9 (9%) corresponding to MH^+.

The boronic acid **115** has also been coupled with a variety of other aryl iodides to provide the corresponding coupled products (Table 9). In general, the reactions were run for 1.5 to three hours, although this is probably not a requirement. The yields observed for the cross coupling with boronic acid **115** were found to be high (63 to 86%). The only side reaction observed was the self-coupling reaction of the boronic acid **115** with itself.

Entry	R-Hal	Product	Time	Conversion(%) Cross coupling product	Conversion(%) Self-coupling product	Yield (%)	Palladium leaching[a] (%)
1		**120**	< 5 min	100	0	86[b]	0.06
2		**121**	1.5 h	100	0	80[b]	0.30
3		**122**	1.5 h	93	7	63[c]	1.37
4		**123**	3 h	90	10	69[c]	0.63

[a] The palladium leaching level correspond to the amount of palladium present as a percentage of the total palladium used.
[b] Isolated yields.
[c] Yields calculated from ^{1}H NMR from a mixture of cross and self-coupling products.

- Table 9 -

For example, after 1.5 hours of reaction the coupling of 3-iodophenyl carboxylic acid with boronic acid **115** gave the coupled product **121** in good yield (80%), and the palladium leaching level found in the product was low (0.30%), as shown in entry 2 of Table 9. A similar result was obtained for 2-iodophenyl carboxylic acid, where the coupled product **122** was formed with a conversion of 93% and 7% of self coupling product, entry 3 of Table 9. This time unexpectedly the palladium leaching level found

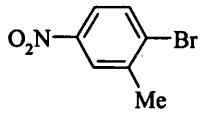
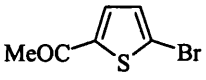
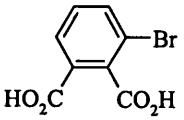
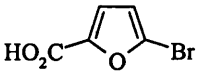
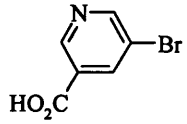
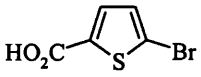
was higher than the one previously observed (1.37%). Finally, the coupling of the alcohol 4-iodophenol was examined, entry 4 of Table 9. The coupled product **123** was formed with a conversion of 90% and 10% of the self-coupling product after three hours of reaction. The formation of the dicarboxylic biphenyls **121** and **122**, and compound **123** were confirmed by the disappearance of the apparent singlet corresponding to the four phenyl protons of boronic acid **115**, and the appearance of once again of a pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the benzene rings.

As previously noted, the reaction of 4-iodophenyl carboxylic acid with boronic acid **115** gave a good result (entry 1, Table 9). The coupling of the corresponding *meta* and *ortho* organohalides showed that the reactivity of the *meta* compound was similar to the *para* compound. In this case no self-coupling product was formed at all, while a small amount of self-coupling product (7% of conversion) was observed for the *ortho* compound **122**. The slow cross coupling reaction in this case can probably be attributed to the steric hindrance due to the close proximity of the carboxylic group and the halide.

** *Cross coupling with bromocompounds*

Bromocompounds, which are generally less reactive than iodoorganohalides have also been tested in the Suzuki cross coupling in the presence of 3 mol% of the reverse phase catalyst and the results are summarised in Table 10. In general, the corresponding coupled products were formed in three hours or less, and good yields were observed, from 70 to 97%. In some cases the self-coupling reaction was also observed. For example the coupling of 5-bromo-5-furoic acid with **115** gave the product **127** with a conversion of 93%, and 7% of the homo-coupling product, entry 4 of Table 10. A low palladium leaching level of 0.36% was observed in the reaction. On the other hand for instance, the

coupling of 2-acetyl-5-bromo-thiophene with boronic acid **115** did not give any self-coupling reaction, entry 2 of Table 10.

Entry	R-Hal	Product	Time	Conversion(%) Cross coupling product	Conversion(%) Self-coupling product	Yield (%)	Palladium leaching [a] (%)
1		**124**	3 h	80	20	70	12.61
2		**125**	3 h	100	0	78[b]	0.31
3		**126**	1.5 h	100	0	97[b]	0.16
4		**127**	1 h	93	7	91[c]	0.36
5		**128**	2 h	75	25	84[c]	0.47
6		**129**	3 h	100	0	85[b]	0.12

[a] The palladium leaching level correspond to the amount of palladium present as a percentage of the total palladium used.
[b] Isolated yields
[c] Yields calculated from ^{1}H NMR from a mixture of cross and self-coupling products .

- Table 10 -

The product was formed in good yield (78%) after three hours of reaction and a low palladium content was observed (0.31%). As the corresponding isolated product **125** was insoluble in most solvents except DMSO in which it is slightly soluble, only the ^{1}H NMR was successful and the synthesis of the product was confirmed by yet again the disappearance of the apparent singlet corresponding to the four phenyl protons of boronic

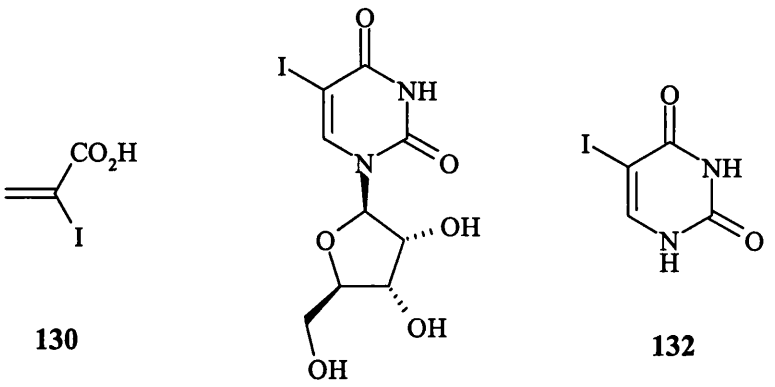
acid **115**, and the appearance of a pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the benzene ring. The electron impact mass spectrum exhibits an ion m/z 245.9 (75%) corresponding to $M^{+\cdot}$. In addition the accurate mass and the infrared spectrum confirmed the formation of the product.

The palladium leaching levels observed for all of the compounds (iodo and bromoaryls) were low, ranging from 0.06 to 0.63% of the total palladium content. The only exception was the coupling of 2-bromo-5-nitrotoluene with **115**. The product **124** was formed with 80% of conversion and in this case a leaching level of 12.61% has been found. This incredibly high metal leaching could be attributed to the fact that the nitro group could be chelating to the palladium. It is important to determine the percentage of metal contamination into the products, especially for possible pharmaceutical applications.

The reactivity of both iodo and bromo reagents in presence of the reverse phase catalyst were found to be quite similar, 69 to 86% for the iodoreagents and 70 to 97% for the bromoreagents.

** *Cross coupling with alkenyliodides*

Although most organohalides that have been chosen as coupling partners with boronic acid **115** are aryl derivatives, a few attempts to react alkenyl halides in the presence of 3 mol% of the reverse phase catalyst have been tried. The three examples examined are shown in Figure 15.



130 131 132

- Figure 15 -

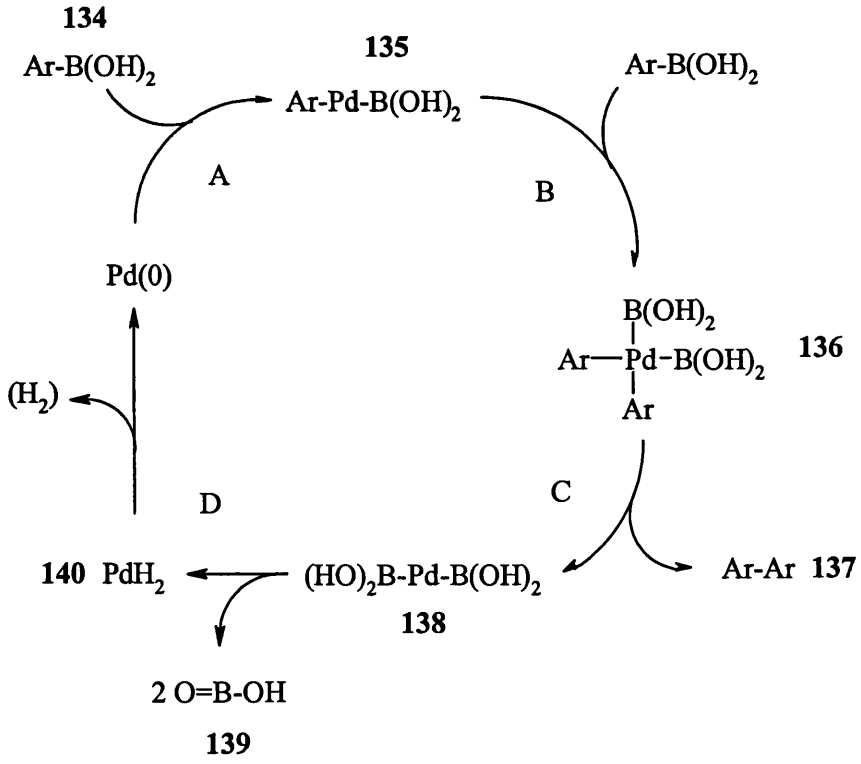
Unfortunately, the coupling of iodoacrylic acid **130** with boronic acid **115** did not give the corresponding product after more than ten hours of reaction. The coupling of 5-iodouracil **132** was also examined and was also unsuccessful. Only the coupling of 5-iodouridine **131** seemed to give the corresponding coupled product **133** with a yield of 28%, which was calculated from a mixture of 2:1 with the self-coupling product. The ^{1}H NMR displays a pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the benzene ring in the product; although the fast atom bombardment mass spectrum exhibits an ion m/z 365.1 (14%) corresponding to M+H, unfortunately the accurate mass on the crude product did not confirm the formation of **133**. Further purification of the product should allow a better analysis.

Alkenyl halides are normally good coupling partners in the Suzuki cross coupling. The low reactivity of iodoacrylic acid **130** may be attributed to the close presence of the carboxylic group next to the iodo moiety. The possible increased reactivity of 5~iodouridine **131** in comparison to iodouracil **132** is probably due to the presence of the sugar moiety in **131**, making it more water-soluble.

** *Self-coupling reaction*

The self-coupling reaction of boronic acids in the presence of a palladium catalyst is a commonly observed side reaction in the Suzuki cross coupling. In general, when the reverse phase catalyst was used in the cross coupling with boronic acid **115**, only small amounts of self-coupling products were obtained (7 – 10% of conversion).

Moreno-Mañas *et al* have been studying the self-coupling reaction and its mechanism as a proper synthetic tool. During their investigation, they have reported the influence of an inert atmosphere on the formation of the homo-coupling product.[128] In their study, they have found that oxygen accelerates the reaction. They also proposed a mechanism for the self-coupling reaction of arylboronic acids, Scheme 34.



- Scheme 34 -

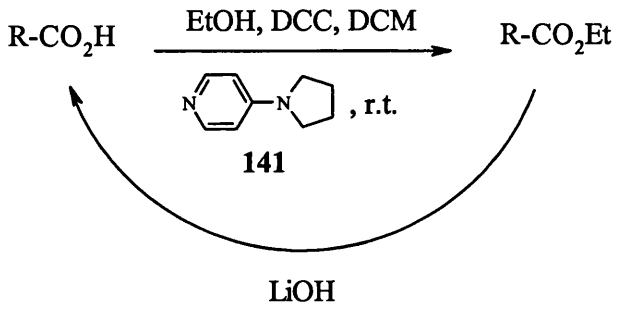
The first step A, consists in the addition of the aryl boronic acid Ar-$B(OH)_2$ **134** to the palladium catalyst. They consider that the oxidative addition and the transmetallation steps merge in this catalytic cycle, although it gives rise to a transfer of an aryl group from the metal boron to the metal palladium catalyst. In step B, a second equivalent of Ar-$B(OH)_2$ is added to the catalytic species Ar-Pd-$B(OH)_2$ **135**. Step C gives the homo coupling product Ar-Ar **137** after a reductive elimination and also the palladium species $(HO)_2$B-Pd-$B(OH)_2$ **138**. As the elimination of $(HO)_2$B-$B(OH)_2$ from **138** is highly unlikely, the formation of the boric derivatives such as metaboric acid **139** (under usual basic condition in the Suzuki coupling **139** would be converted into borate). Finally, the intermediate PdH_2 **140** can release hydrogen or reduce oxidants present in the reaction media such as the oxygen in a normal air atmosphere.

However, even when a number of reactions using the glass bead catalyst were realised with rigorous exclusion of oxygen, the self-coupling product was still formed in similar yields. There have been in the literature other examples of homogeneous catalyses that have reported the influence of oxygen in the self coupling reaction for the Suzuki cross coupling.[44,129] it seems then possible that in the case of the reverse phase catalyst, the homo coupling reaction involves different pathways for the formation of this side product than those already reported.

Another attempt to decrease the amount of self-coupling product was investigated. The general reason for the formation of this side product would generally be attributed to the fact that the boronic acid **115** would react faster with itself than with the corresponding organohalide. The cross coupling would therefore be slower in comparison. Consequently to overcome this problem, a slow addition of the boronic acid **115** to the reaction mixture

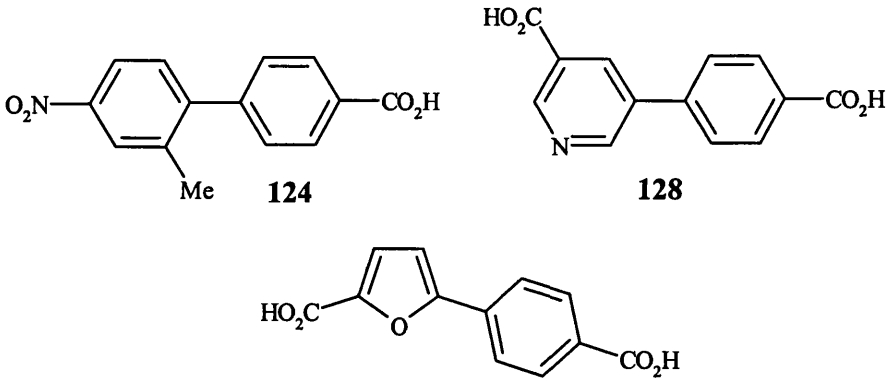
was realised. For example, boronic acid **115** was slowly added into the reaction containing 5-bromo-5-furoic acid and the supported catalyst, but unfortunately the amount of self-coupling product observed did not decrease and even a higher conversion of the side product was observed (22%).

For most products collected as a mixture of the self-coupling and the cross coupling product or those just containing impurities, the coupled product was isolated by esterification. Initial attempts to esterify the mixture using $SOCl_2$, with or without the presence of pyridine,[130] did not work and very low conversions were observed.



- Scheme 35 -

The esterification of both cross and self coupling products at room temperature in the presence of *N,N*-dicyclohexylcarbodiimide, ethanol and 4-pyrrolidinopyridine **141** was examined,[131] Scheme 35. This method was applied to three products **124, 128** and **127,** resulting from the coupling of boronic acid **115,** Figure 16.



- Figure 16 -

The corresponding esters were produced in moderate to good yield, and the coupled products were then isolated and saponified to regenerate the pure cross coupling product,[132] for full analysis and characterisation, Table 11.

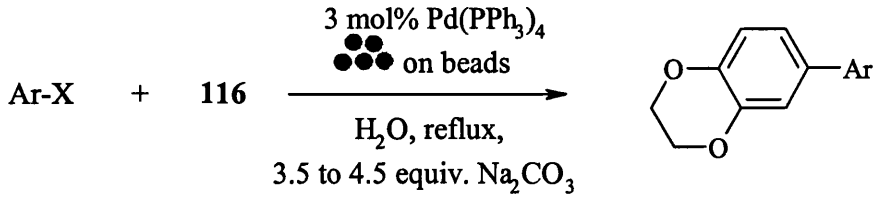
Product	Esterification Isolated yield (%)	Saponification Isolated yield (%)
124	66	41
127	19	56
128	83	53

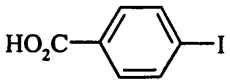
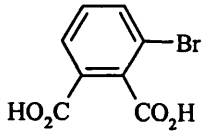
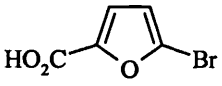
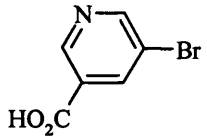
- Table 11 -

For example, the esterification of compound **124** into the corresponding mono ethylester was realised in good yield (66%). After purification by column chromatography and saponification with LiOH, the product **124** was isolated after acidification in 41% yield. The formation of product **124** was confirmed by the accurate mass spectrum.

- *Boronic acid 116*

Boronic acid **116** has been coupled to a few organohalides under the previous conditions, as shown in Table 12. As previously observed the reactivity of iodo and bromo aryls is quite similar in these examples.



Entry	Ar-X	Product	Time	Yield (%)	Palladium leaching (%)
1		**142**	3 h	96	3.30
2		**143**	2 h	47	2.52
3		**144**	2 h	85	2.75
4		**145**	2.5 h	26	2.90

- Table 12 -

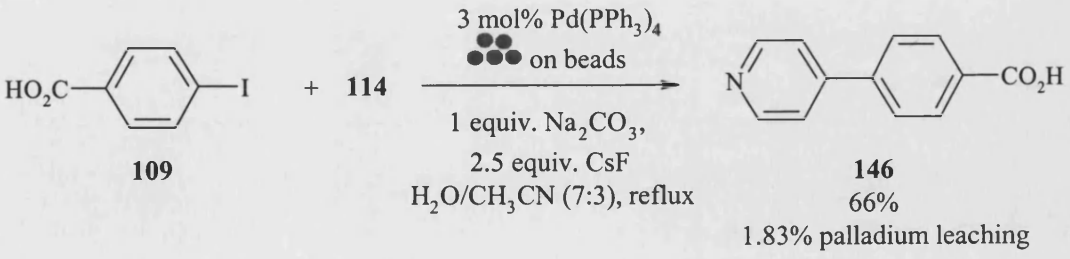
Although the water solubility of boronic acid **116** is lower than boronic acid **115**, the isolated yields obtained are moderate to good after only three hours or less of reaction (Table 12). For example the coupling of 4-iodobenzoic acid **109** with boronic acid **116**, entry 1 of Table 12, gave the coupled **142** in 96% of yield after 3 hours of reaction. Only the yield observed for the coupling of 5-bromonicotinic acid was low 26%, entry 4 Table

12. In addition, as a general observation no self-coupling product was observed when this boronic acid was used.

The palladium leaching detected in the final products was ranged from 2.75 to 3.30%, which is much higher than that observed for the previous boronic acid **116**. The increase in the metal leaching is probably due to the fact that the final product is less water-soluble and the palladium catalyst resides then preferably with the product.

- *4-Pyridinylboronic acid **114***

The reaction with 4-pyridinylboronic acid **114** was also examined. The first attempt of cross coupling 4-iodobenzoic acid with boronic acid **114** in water did not provide any product under the previous conditions. This was probably due to a poor solubility of the boronic acid. Consequently in order to get the best reactivity, it was necessary that both reagents should be well solubilised. When the reaction was run exclusively in water, the reagents were solubilised by adding extra equivalents of base. Therefore in addition, it was important to find a system of solvents that would allow the good solubility of both reagents. Acetonitrile was chosen as a co-solvent, as it has been reported in similar reactions.[133]



109 **146**
66%
1.83% palladium leaching

- Scheme 36 -

The most successful results were obtained using a water/acetonitrile (7:3) mixture as solvent, with one equivalent of Na_2CO_3 to deprotonate the carboxylic acid group present in the organohalide, and 2.5 equivalents of CsF to promote the Suzuki reaction, Scheme 36. The corresponding coupled product **146** was isolated in good yield (66%) in the presence of 3 mol% of the reverse phase catalyst. The formation of the product was confirmed by the ^1H NMR spectrum that displays a pair of doublets (AA'BB' system) demonstrating the *para*-substitution of the pyridine ring and an apparent singlet corresponding to the four protons of the *para*-substituted benzene ring. Although there is a difference with the melting point reported in the literature, the accurate mass measurement was obtained and confirmed the formation of product **146**.

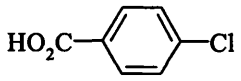
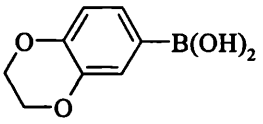
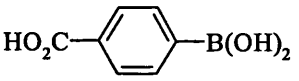
Several others bases such as K_3PO_4 or NaOH have also been tested to promote the reaction. Unfortunately the yields obtained were at low 6% for K_3PO_4 and 28% for NaOH after 2 hours of reaction, and in some cases the reverse catalyst seems to get damaged under these conditions.

In some cases, the higher efficiency of CsF in promoting the Suzuki reaction in comparison to other more basic reagents have also been previously reported,[134] and these results are explained by the high affinity of the fluoride ion for the boron, and the considerable stability of the by-product formed, a fluoroborate ion.

Also, it was interesting to note that the leaching level was higher than those generally observed for boronic acid **115**, Table 9. It was believed that in this case the pyridine might be able to act as a ligand to draw palladium into the aqueous layer. Additionally, the lower polarity of the water/acetonitrile solvent may have an effect on partitioning.

- *Chloro compounds*

Although chloro compounds are in general less reactive than iodo or bromo organohalides, the last decade has seen the emergence of various methodologies for the cross coupling of chloro compounds.[26] The reaction of chlorinated arenes has then been briefly investigated in the presence of the reverse phase catalyst. Whilst aryl iodides and aryl bromides were satisfactory coupling partners in the presence of the catalyst, only small amounts of coupled product (6%) were obtained when using 4-chlorobenzoic acid with boronic acid **116** (entry 1, Table 13) and no product formed at all with boronic acid **116**, entry 2 of Table 13.

Entry	Ar-Cl	Ar'-B(OH)$_2$	Time	Conversion (%)	Yield (%)
1			20.5 h	11	6
2			3 h	0	0

- Table 13 -

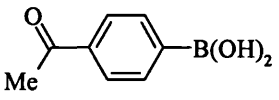
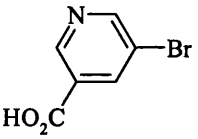
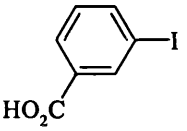
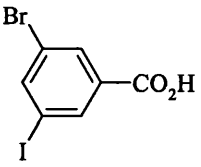
The reverse phase glass beads methodology could, in principle, be applied to other non~polar ligands. For example alternative non-polar ligands used for catalysts such as palladacycles have not been examined, and could give interesting results especially since they show really high efficiency, as previously examined in section **1.3.3**.

- *Other boronic acids*

A series of non-water-soluble boronic acids has also been coupled with water-soluble and non-water-soluble organohalides. The results are shown below successively for each boronic acid. In contrast to the coupling of pyridin-4-ylboronic acid **114** where a mixture of acetonitrile and water was necessary for the reaction, in the following examples the reactions were achieved exclusively in water. Finally no self-coupling product was observed at all for all these boronic acids.

** *Boronic acid 113*

4-Acetylphenylboronic acid **113** was coupled to three organohalides in the presence of the supported catalyst (1 and 3 mol%), as shown in Table 14. All the cross coupling reactions were complete in two or three hours and in high yields (81% to 84%). Also all the products, which contain at least one carboxylic group, were easily isolated by acidification with HCl and after filtration.

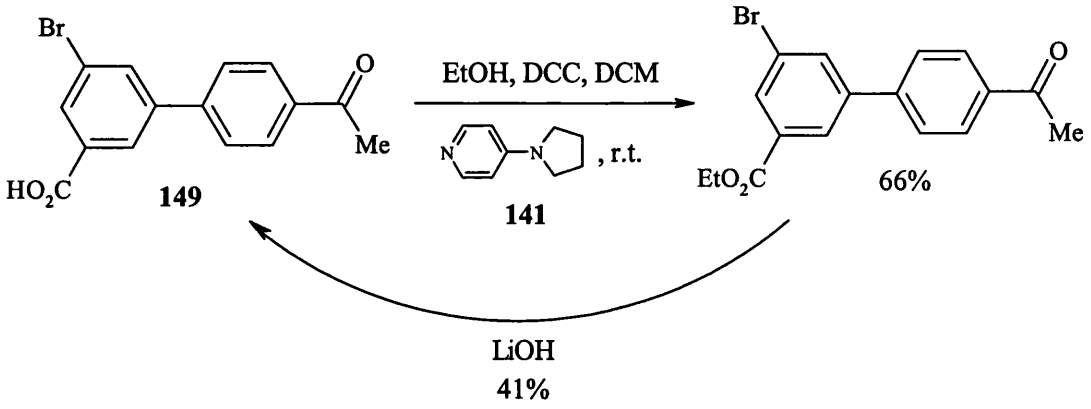
Entry	Ar-B(OH)$_2$	Product	Ar-Hal	Time	Yield (%)	Palladium leaching (%)
1		**147**		2 h	84[b]	0.19
2		**148**		3 h	81[b]	< 0.50
3		**149**		3 h	83[a, c]	< 0.03

[a] Yields calculated from ^{1}H NMR

[b] 1 mol% of catalyst was used; [c] 3 mol% of catalyst was used.

- Table 14 -

For example, the coupling of 5-bromonicotinic acid with **113** in the presence of 1 mol % of the reverse phase catalyst gave the corresponding coupled product **147** in good yield (84%), entry 1 of Table **13**. The palladium content analysed in the product was low, 0.19%. Also the coupling of the 3-iodobenzoic acid gave similar results, with high yield (81%) and a palladium leaching level below 0.50%, entry 2 of Table **13**. Finally, it was interesting to compare the reactivity of C-I with C-Br when they are present in the same molecule, in the presence of the supported catalyst and in the conditions set previously. 3~Bromo-5-iodobenzoic acid was then refluxed for three hours with boronic **113** in the presence of 3 mol% of the supported catalyst. The coupled product was produced in 83% of yield, calculated from the ^{1}H NMR spectrum and the product was purified by esterification and saponification as previously described for boronic acid **115** to give the pure coupled product, as shown in Scheme 37. The palladium content found in the product was below 0.03%, entry 3 of Table 14.

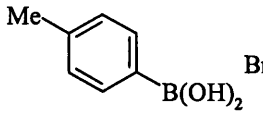
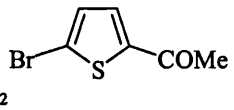
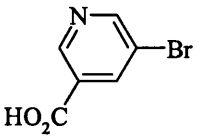


- Scheme 37 -

The formation of the product **149** was confirmed by accurate mass measurement. The result for the cross coupling reaction of boronic acid **113** showed that although the bromo and the iodoreagents seem to have similar reactivity, the C-I bond still reacts preferentially.

*** Boronic acid 117*

4-Methylbenzeneboronic acid **117** was coupled to two different bromoreagents, as shown in Table 15. The two corresponding coupled products were formed in moderate to good yield (30 and 82%) in the presence of 1 mol% of the supported catalyst after two hours of reaction. In the case of the coupling of 2-acetyl-5-bromothiophene with **117**, entry 1 of Table 15, the product **150** was completely insoluble in water and was isolated in good yield (82%) after purification by column chromatography.

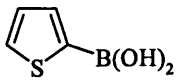
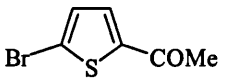
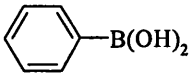
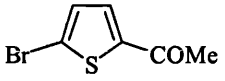
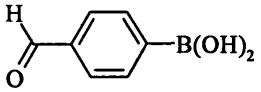
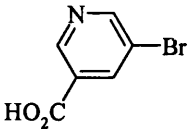
Entry	Ar-B(OH)$_2$	Ar-Hal	Product	Time	Yield (%)	Palladium leaching (%)
1			**150**	2.5 h	82	< 0.06
2			**151**	2.5 h	30	< 0.09

- Table 15 -

The coupled product **151** resulting from the cross coupling of 5-bromonicotinic acid with **117** was isolated easily in 30% yield, after acidification and filtration. Low palladium leaching levels were observed in both coupled products (below 0.06 and 0.09%).

*** Other boronic acids, 1, 118, 119*

Finally three other boronic acids have been tested for the efficiency of the supported catalyst in water. All the reactions were carried out in the presence of 1 mol% of the supported catalyst. In these last examples, the yields obtained for the corresponding coupled products were variable. For example the coupling of 4-formylphenylboronic acid **119** with 5-bromonicotinic acid gave the highest yield 68%, entry 3 of Table 16. This is probably due to the presence of the carboxylic acid group in the molecule, which makes it more water-soluble. The palladium content found in the product was low (0.14%).

Entry	Ar'-B(OH)$_2$	Ar-Hal	Product	Time	Yield (%)	Palladium leaching (%)
1			**152**	2.5 h	34	< 0.03
2			**153**	3 h	53	< 0.02
3			**154**	2.5 h	68	0.14

- Table 16 -

The couplings of 2-thienylboronic acid **118** and phenyl boronic acid **1** with 2-acetyl-5-bromothiophene were examined and both products **152, 153** were isolated in moderate yields after purification by column chromatography. The palladium leaching levels were low (below 0.02 and 0.03%), Table 16.

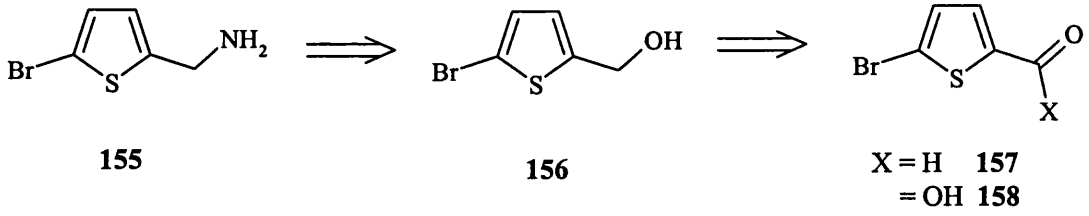
- *Different mol% for the supported catalyst*

The supported catalyst has been used in the Suzuki cross coupling of various reagents and generally the reactions were carried out in the presence of 1 or 3 mol% of the catalyst. The coupled products were produced in moderate to excellent yields depending on the substrate. As the catalyst seemed to be as efficient when only 1 mol% was used, the use of a more catalytic quantity of the catalyst was quickly examined. The cross coupling of 4-iodobenzoic acid **109** with 4-carboxyphenylboronic acid **115** was carried out in the presence of 0.03% of catalyst. The mixture was refluxed for 20 hours (which is probably not a requirement) and the product **120** was isolated in good yield (91%).

2.3.2.3 Synthesis of one starting material

All the starting materials used previously were commercially available compounds and most of them contain at least one carboxylic, alcohol, nitro or secondary amino group. Compound **155**, (5-bromo-2-thienyl)methylamine, was an interesting reagent for the catalysed cross coupling using the reverse phase catalyst in water, as it is a five membered heterocycle containing a primary amino group and this type of organohalide has not been considered yet.

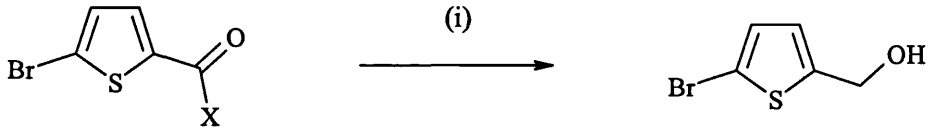
The retro-synthetic analysis of compound **155** led to Scheme 38, where alcohol **156** could be synthesised by reducing the corresponding carboxylic acid **158** or aldehyde **157**. Then conversion to compound **155** could be obtained by following a typical methodology for the synthesis of primary amine.



155 **156** X = H **157**
= OH **158**

- Scheme 38 -

Attempts to reduce 5-bromo-2-thiophene carboxylic acid **158** to the corresponding alcohol **156** using several reducing agents has been examined, but the product was only isolated in low yields when either $LiAlH_4$ or B_2H_6 were used. Only the reduction of aldehyde **157** with $NaBH_4$ gave the isolated alcohol **156** in 50% of yield, Table 17. The formation of the alcohol **156** was confirmed by ^1H NMR, with the appearance of a broad singlet at δ 2.75 ppm corresponding to the proton of the hydroxy group.



X = H **157**
= OH **158**

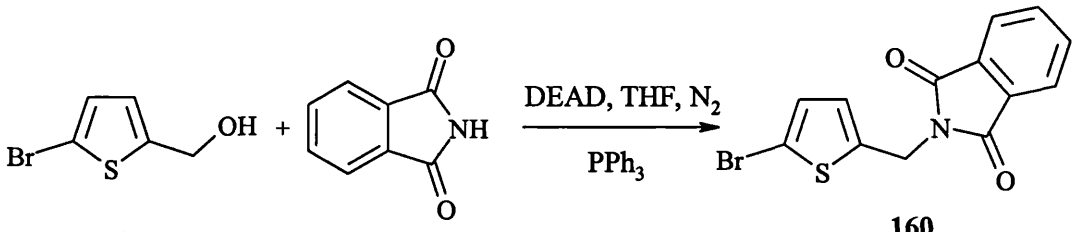
156

(i) $LiAlH_4$, THF, N_2, reflux or B_2H_6.THF, N_2, 0 °C to r.t. or $NaBH_4$, N_2, MeOH, r.t.

X	Reducing agent	Time	Isolated yield (%)
OH	$LiAlH_4$	2 h	0
OH	B_2H_6	overnight	20
H	$NaBH_4$	5 h	50

- Table 17 -

The formation of amine **155** from alcohol **156** has then been investigated following a Mitsunobu type reaction using phthalimide as the nucleophile,[135] Scheme 39. Unfortunately after three days of reaction, no product was isolated with this method. The ^1H NMR displayed a mixture of products and starting materials.



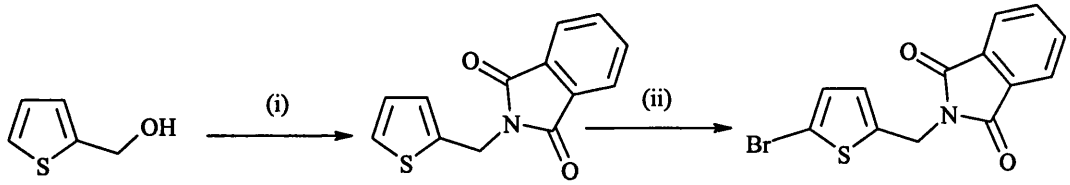
156 **159** **160**
0%

- Scheme 39 -

The direct reaction of the aldehyde **157** with ammonium formate following a reported procedure did not give better results.[136] The pure alcohol **156**, which was obtained by either column chromatography or by distillation under reduced pressure, has revealed to

be unstable probably due to the presence of OH group in the molecule. Only the ^{1}H NMR of the degradation product was obtained and it displayed two pairs of doublets (AB system) in a ratio 3:1 demonstrating the disubstitution of two different types of thiophene rings. Also no proton from the hydroxy group was observed, but a singlet (in a ratio of 3:1) corresponding to the proton of an aldehyde was observed at δ 9.70 ppm.[137]

Another approach was then examined. This time the starting molecule was the alcohol **161**. The synthesis of compound **160** has been reported using another methods, as shown in Scheme 40. As it was originally reported,[138] the synthesis started from the 2-(chloromethyl)thiophene. Unfortunately the conversion of 2-thienylmethanol **161** with $SOCl_2$ with or without pyridine did not give the corresponding chlorocompound. The alcohol **161** was then directly used in the synthesis to react with phthalimide following the procedure described previously in Scheme 39. Finally, the bromide was introduced into the molecule at the 5-position, in the presence of acetic acid and bromine, step (ii) of Scheme 40.



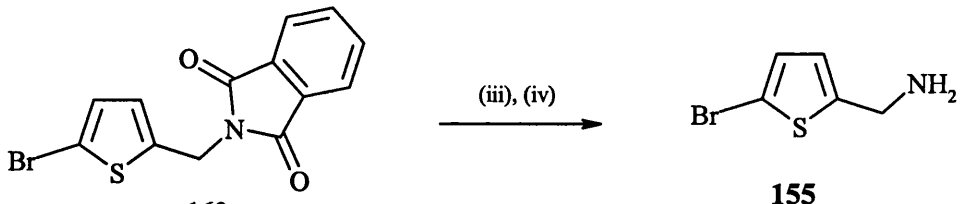
161 **162** 35% **160** 97%

(i) PPh_3, DIAD, **159**, r.t., THF, 3 days
(ii) AcOH, Br_2 r.t., overnight

- Scheme 40 -

First compound **162** was isolated as a colourless solid in 35% of yield. The synthesis of this product was confirmed by ^{1}H NMR, with the disappearance of the broad singlet at δ

2.75 ppm. Compound **160** was then produced in good yield (97%) by treatment of **162** with bromine in acetic acid. The formation of **160** was confirmed by ^{1}H NMR with the appearance of a pair of doublets (AB system) demonstrating the disubstitution of the thiophene ring. Finally the reduction of compound **160** was carried out in ethanol with NH_2NH_2 following a reported procedure.[139] In the step (iv), the ammonium salt of **155** was formed by addition of HCl to the reaction mixture, to afford after a basic treatment the amine **155** as a white cream solid in 32% yield, Scheme 41. The synthesis of compound **155** was confirmed by accurate mass and by ^{1}H NMR, which displayed a broad singlet at δ 1.69 ppm corresponding to the protons from the amino group.

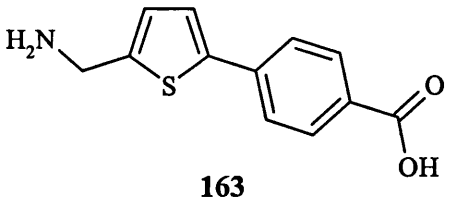


160 **155** 32%

(iii) $NH_2NH_2.H_2O$, EtOH, reflux, 1 h
(iv) HCl, reflux, 30 min.

- Scheme 41 -

Final compound **155** would be tested as a reagent in the Suzuki reaction in the presence of the supported catalyst. For example the cross coupling of **155** could be considered with the boronic acid **115** to give the product **163**, Figure 17.

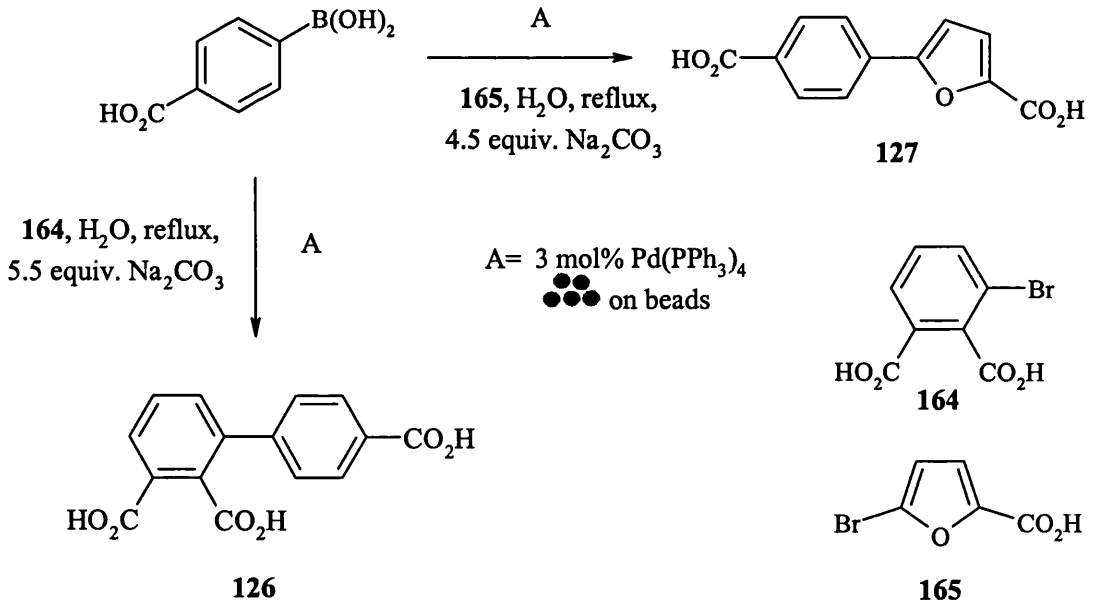


163

- Figure 17 -

2.3.2.4 Recycling of the catalyst

The recycling of the reverse phase catalyst has been briefly examined for the coupling of boronic acid **115** with 5-bromo-2-furoic **165** acid and 4-bromophthalic acid **164**, as shown in Table 18. The reaction conditions, which were the same for each run, are described in Scheme 42.



- Scheme 42 -

The recycled catalyst was used in a repeated reaction with some loss of activity. For example, the synthesis of **126** was carried out twice using 3 mol% of the supported

catalyst in water at reflux, and 97% then 94% of isolated yields were observed successively. Similar results were obtained for the synthesis of **127**, after two uses the yield dropped from 91% to 66%, which is still a respectable yield. A third use of the catalyst was carried out and after 23 hours of reaction no product was formed, as shown in Table 18. All the palladium leaching levels found in the products were below 1 ppm.

Product	Time	Number of uses	Yield (%)
127	1.5 h	1	97
127	1.5 h	2	94
126	1 h	1	91[a]
126	17 h	2	66[a]
126	23 h	3	0[b]

[a] Yields calculated from ^{1}H NMR from a mixture of cross and self coupling products.
[b] The starting materials were recovered.

- Table 18 -

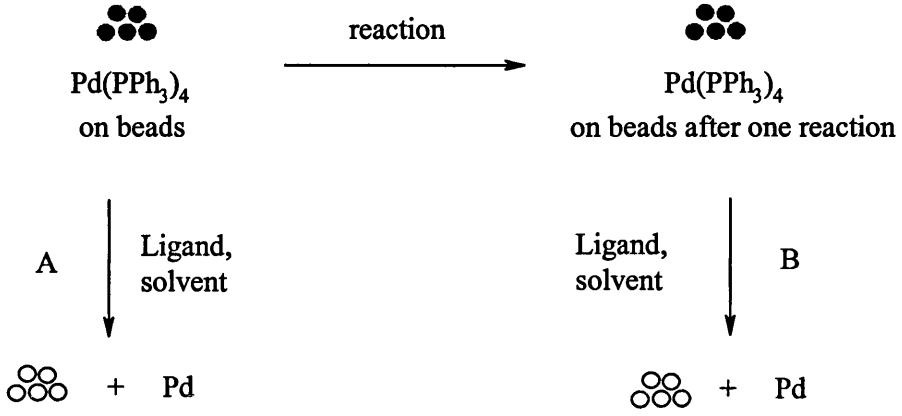
The viability of the reverse phase catalyst as a new heterogeneous catalyst for Suzuki cross coupling in industry would require that the catalyst should have a long life and this could be achieved by understanding why the loss of activity occurred after only two reactions.

The first reason could be due to the fact that the supported catalyst is oxidised by the oxygen present in the air, either when it is handled or during the reactions if the conditions do not rigorously exclude air. The recycling of the catalyst and in general the reactions have been carried out under rigorous oxygen free conditions and also under normal air atmosphere. The results showed that under both conditions similar reactivity

for the reverse phase catalyst was observed, which would mean that the catalyst is probably not sensitive to the presence of oxygen and that the reactions can be carried out without a nitrogen atmosphere.

Another cause of the low recycling of the catalyst could be attributed to the slow leaching of the ligands, which would then result in the formation of inactive Pd(0). The reverse phase catalyst is composed of $Pd(PPh_3)_4$, so in this case the ligand triphenylphosphine may be leaching into the reaction mixture. During the work up of a typical reaction using the reverse phase catalyst, phosphine oxide was observed when the aqueous solution was extracted with diethyl ether. The formation of phosphine oxides is generally due to the oxidation of phosphine in the presence of water; this explanation was confirmed by the isolation of phosphine oxide when a mixture of water and the reverse phase catalyst were refluxed for a few hours. It would be interesting to find out how many equivalents of phosphine are leaching into the solution after each use of the catalyst.

Although heterogeneous catalysis holds many advantages, the investigation into more details of the mechanistic properties of the catalyst is a real challenge, as there could be different types of active sites on the catalyst. Nevertheless, it would be interesting to understand more the reasons of the loss of activity. An idea would be to try to draw the palladium species into a solution to find out more about its oxidation state before reaction (step A) and after reaction (step B), as shown in Scheme 43.



- Scheme 43 -

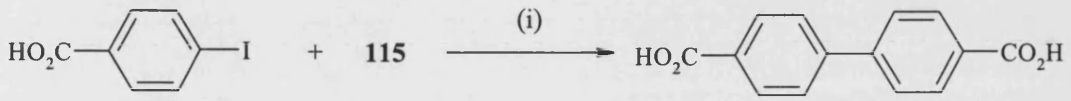
Also, the achievement of removing the palladium species from the derivatised silica after reactions would be a good way to recycle the solid support, which could then be loaded again with fresh palladium catalyst. The preliminary results were carried out on step A, unfortunately the stirring of the supported catalyst in several solvents such as cyclohexane, DCM or THF in the presence of the phosphine ligand $P(C_6H_{10})_3$ did not gave any important leaching of the palladium into the organic phase. The use of bidentate ligands to draw the palladium should also be considered.

2.3.2.5 Comparison of the supported catalyst with $Pd(PPh_3)_4$

Although the reverse phase catalyst has shown so far a good reactivity for the Suzuki cross coupling in water, it was important to ensure that the reaction was not proceeding as efficiently in the absence of the silica support. Therefore the synthesis of three products were chosen to compare the efficiency of the supported $Pd(PPh_3)_4$ on the reverse support and $Pd(PPh_3)_4$ by itself. All the conversions expressed in the graphs were calculated from the ^1H NMR spectra of the resulting product.

- For the synthesis of compound **120**

The reactions were carried out as previously described in section **2.3.2.2**, and samples were taken throughout the reactions to follow the completion of the cross coupling reaction.

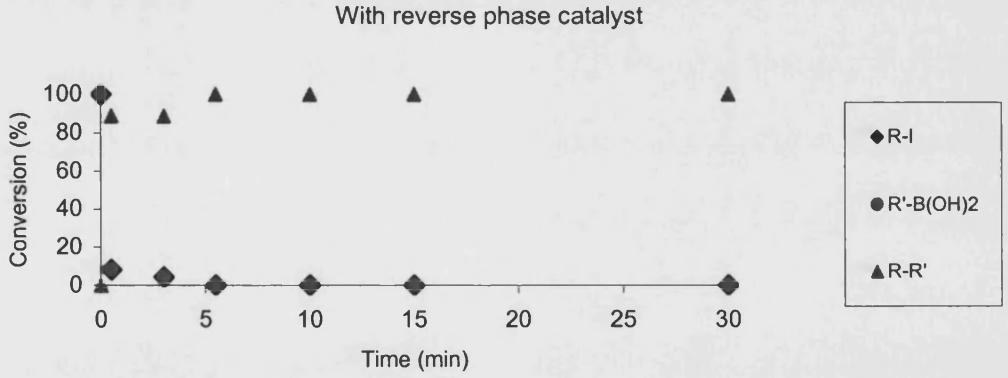


109 **120**

(i): 3 mol% of $Pd(PPh_3)_4$ or supported catalyst, H_2O, reflux, 4.5 equiv. Na_2CO_3

- Scheme 44 -

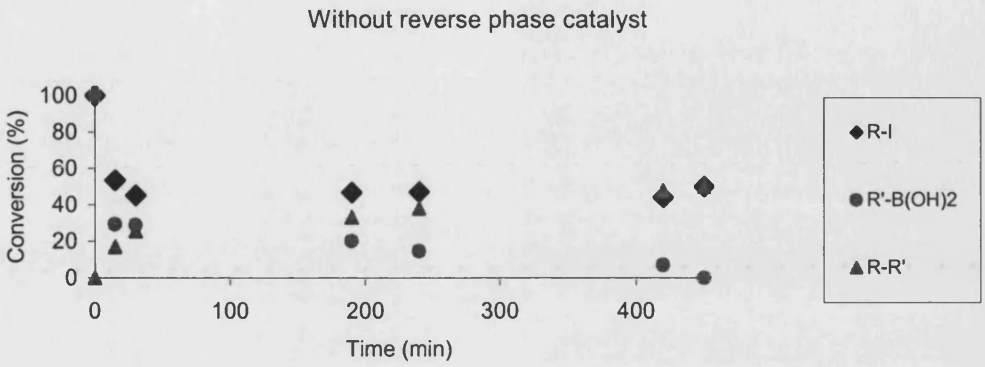
The results are shown in Graph 1 for the reaction in the presence of the supported catalyst and in Graph 2 for the reaction in presence of the conventional catalyst $Pd(PPh_3)_4$.



- Graph 1 -

Graph 1 showed that the presence of the glass beads has a strong influence on the rate of the reaction. After only five minutes, the reaction was proceeding in less than 5 minutes

with more than 88% conversion to the product. The absence of self-coupling product was confirmed by the fact that no starting materials were recovered at the end of the reaction.

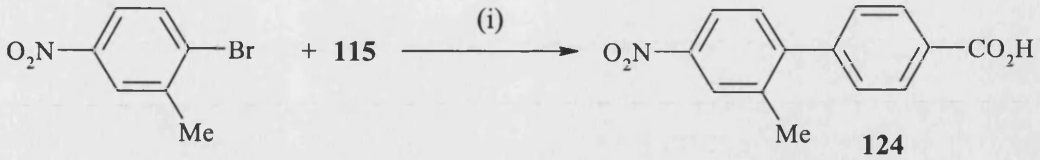


- Graph 2 -

In comparison, the Suzuki cross coupling of 4-iodobenzoic acid **109** with boronic acid **115** using the conventional catalyst $Pd(PPh_3)_4$ gave only 50% of conversion after 7.5 hours of reaction, while in less than five minutes the reaction was almost complete when using the supported catalyst. It should also be noticed that in the first hour of reaction the product was formed from both cross and self coupling reaction since the percentage of the boronic acid **115** was decreasing faster than the percentage of 4-iodobenzoic acid. Then the cross coupling reaction slowed down and only the self-coupling reaction was proceeding until complete disappearance of the boronic acid **115**.

- For the synthesis of compound **124**

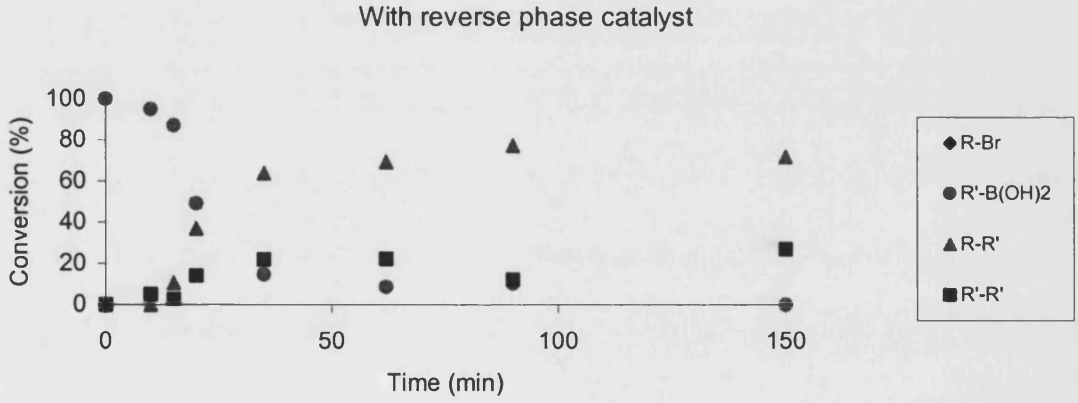
The coupling of 2-bromo-5-nitrotoluene with 4-carboxyphenylboronic acid **115** was then examined, Scheme 45.



(i): 3 mol% of $Pd(PPh_3)_4$ or supported catalyst, H_2O, reflux, 3.5 equiv. Na_2CO_3

- Scheme 45 -

First the results obtained for the reaction in the presence of the supported catalyst are shown in Graph 3. It should be noticed that the reaction was complete after only 1.5 hours and that the self-coupling product was formed in about 20% of conversion in the first 30 minutes. The 2-bromo-5-nitrotoluene reagent does not appear in Graph 3 as it was washed away in the work up when extracted with diethyl ether.



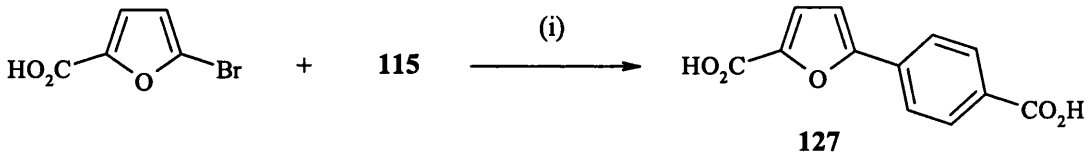
- Graph 3 -

The cross coupling reaction was then carried out in water with only $Pd(PPh_3)_4$ as catalyst and the reaction was refluxed for more than eleven hours. The study showed that the reaction did not work at all, only the boronic acid was recovered throughout the reaction by precipitation and no self-coupling product was observed either. A reason for this result

could be attributed to the fact that the nitro group would chelate to the palladium, as previously mentioned in section **2.3.2.2.** However in that case, the presence of the supported catalyst seemed to enable this cross coupling reaction.

- For the synthesis of compound **127**

Finally, the coupling of boronic acid **115** with 5-bromo-2-furoic acid was investigated, Scheme 46. The results obtained for the coupling in the presence of the supported catalyst are presented in Graph 4.

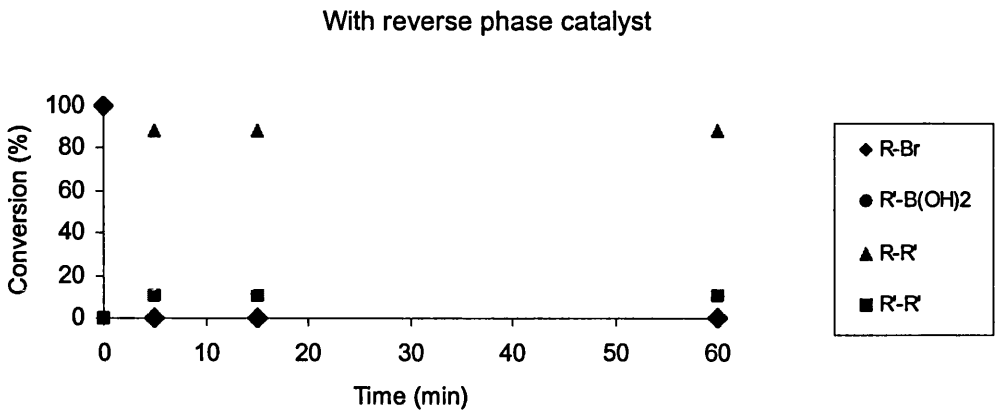


127

(i): 3 mol% of $Pd(PPh_3)_4$ or supported catalyst, H_2O, reflux, 4.5 equiv. Na_2CO_3

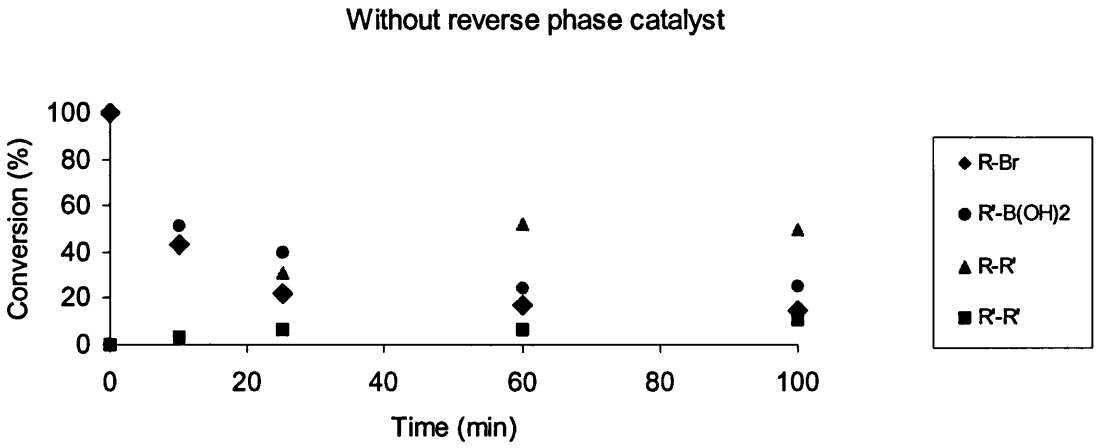
- Scheme 46 -

In this case the cross coupling was complete in five minutes and a conversion of 90% was observed. Once again the self-coupling product was formed up to its maximum (10% of conversion) in the early stage of the reaction.



- Graph 4 -

In the absence of the supported catalyst, the coupled product **127** was only formed in about 50% of conversion and equal amounts of self-coupling product (10% of conversion) were observed in both reactions. After one hour the cross coupling reaction seems to stop, as both starting materials were still present at the end of the reaction, as shown in Graph 5.



- Graph 5 -

In conclusion, the comparison of the supported catalyst with $Pd(PPh_3)_4$ in aqueous solution gave some interesting results. The supported catalyst has proven to be of higher efficiency and in all cases the cross coupling reaction was complete in five minutes, except 1.5 hours for the nitro reagent.

The increased reaction rate can be attributed to the large contact area between the water and the organic phase when beads are present. Also when $Pd(PPh_3)_4$ was supported on the glass bead, it seemed to be 'protected' from the nitro group and the corresponding coupled product **124** was formed in good yield (70%).

Whether the cross coupling reaction was catalysed by the supported catalyst or the conventional catalyst $Pd(PPh_3)_4$, the self coupling reaction, when observed, seemed to occur mainly at the beginning of the reaction and then either slow down or consume all the boronic acid. However, among all the boronic acids that have been studied in the Suzuki cross coupling in the presence of the supported catalyst, only the reaction with 4~carboxyphenylboronic acid **115** gave some self coupling product.

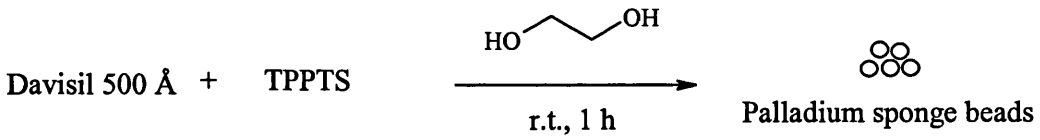
2.3.2.6 Sponge beads

2.3.2.6.1 Introduction[105]

The glass bead technology has been successively applied to various catalytic reactions. In these previous contexts, the glass bead and its surrounding were able to retain the catalyst throughout the reactions, resulting in low leaching of the metal into the solution. From these results, it was interesting to investigate whether the glass beads could be turned into an efficient method to remove transition metals from a solution at the end of a reaction. The use of the glass beads as sponge beads to clean up any palladium present in a solution has then been examined within the group. Before that, only a few examples have been

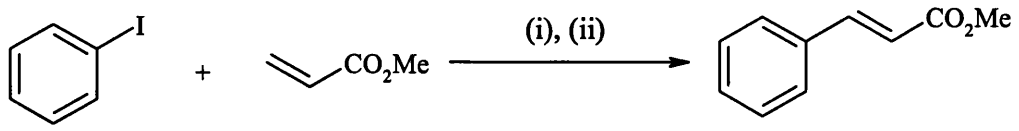
reported in the literature for the removal of palladium from reaction solvent. A common reagent used for the removal of $Pd(PPh_3)_4$ is palladium on charcoal, but a considerable amount is usually necessary to achieve good removal. Also, Feng *et al* have reported that the use of mesoporous silica materials, which contain functionalised organic monolayers of propylsilane, are efficient in removing mercury and other heavy metals from both aqueous and organic waste streams.[140] Degussa has reported a metal-absorbing resin called Deloxan THP II which contains organofunctional polysiloxanes bearing thiourea or thioether groups to recover metals such as rhodium, palladium and platinum from highly diluted product or waste streams.[141]

The work carried out in the group was focused on the use of normal phase glass beads to remove palladium from reaction mixtures. The sponge beads were prepared by mixing for one hour the polar ligand TPPTS **25** with Davisil beads (500 Å) in ethylene glycol, Scheme 47.



- Scheme 47 -

The resulting palladium sponge beads were a free-flowing powder, which was easy to add and then filter. This technique has been applied to a few palladium-catalysed reactions and significantly low palladium leaching levels were observed. One example is the Heck coupling of iodobenzene **71** with methyl acrylate **86** which has been carried out in toluene in the presence of $PdCl_2$ and gave the corresponding product **87** in good yield, as shown in Scheme 48.



71 **86** **87**
71%

(i): 1mol% $PdCl_2$, 2 mol% PPh_3, NEt_3, Toluene, 3 h
(ii): palladium sponge beads, stirring r.t., 10 min.

- Scheme 48 -

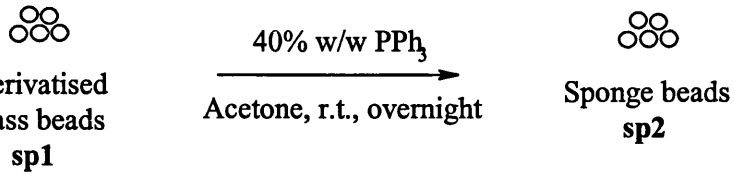
At the end of the reaction the sponge beads were then added to the solution and the mixture stirred for ten minutes. The filtrate was then analysed and no palladium was detected in the product. The possibility of removing metal transitions from any solution has great ecological potential, and in addition the use of a heterogeneous support is a further advantage.

2.3.2.6.2 Results

The use of the sponge beads to remove palladium from organic solvents has been examined as previously reported. In this study, the use of the reverse phase glass beads has been mainly used in the Suzuki cross coupling of various reagents exclusively in water. The interest was then to transpose the use of the glass bead as a catalyst into a palladium sponge bead that would be able to remove the metal from any aqueous solutions.

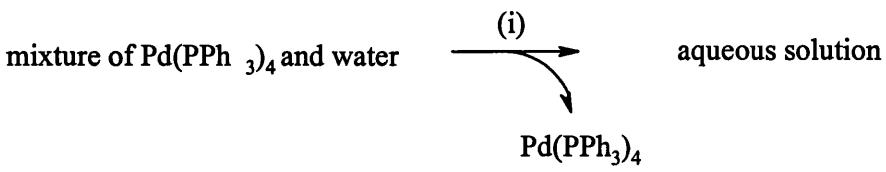
Two different types of sponge beads were then prepared. The first type of sponge beads was the derivatised glass bead, denoted **sp1**, which has been used to try to remove the palladium from aqueous solutions. The normal derivatised glass beads (**sp1**) were tested as potential palladium sponge beads, since the reactions are carried out in water and most of the reagents and products are water-soluble, the addition of triphenylphosphine to trap

the metal may not be necessary. The second type was prepared easily by adding 40% w/w of triphenylphosphine to the derivatised glass bead in acetone, and the sponge beads **sp2** were collected as a white powder, Scheme 49.



- Scheme 49 -

To have an idea of the efficiency of the sponge beads prior to its direct use as a work-up in reactions, a simple test in water was carried out. To a mixture containing the catalyst $Pd(PPh_3)_4$ and water under nitrogen, was added either sponge beads **sp1** or **sp2**, and the mixture was stirred for 10 minutes, Scheme 50. The mixture, which was initially yellow, became more colourless while the sponge beads were getting yellow. The mixtures were then filtered and the solutions analysed for palladium content. It was also important to compare the sponge beads method to a traditional way of extracting aqueous solution. Therefore a mixture containing the catalyst $Pd(PPh_3)_4$ and water was extracted with diethyl ether either once or twice and the aqueous solution was then analysed, as shown in Scheme 50.



(i): **sp1** or **sp2** or extraction with Et_2O

- Scheme 50 -

The results obtained from these tests are reported in Table 19. First, the aqueous solutions resulting from simple extractions with diethyl ether were analysed. After one extraction the palladium leaching level observed was 0.83% of the maximum amount of the palladium that could leach. When two extractions were carried out the percentage dropped to 0.14%. The efficiency of the sponge beads was then examined and the sponge beads were added in a ratio of 1:10 with respect to the mass of catalyst stirred into the aqueous solution. The palladium leaching level found in the solution was inferior to 0.03%, after the sponge beads **sp1** were added. When **sp2** was added in the same ratio (1:10) to the mixture of $Pd(PPh_3)_4$ and water, the palladium leaching level dropped below 0.003%, as shown in Table 19.

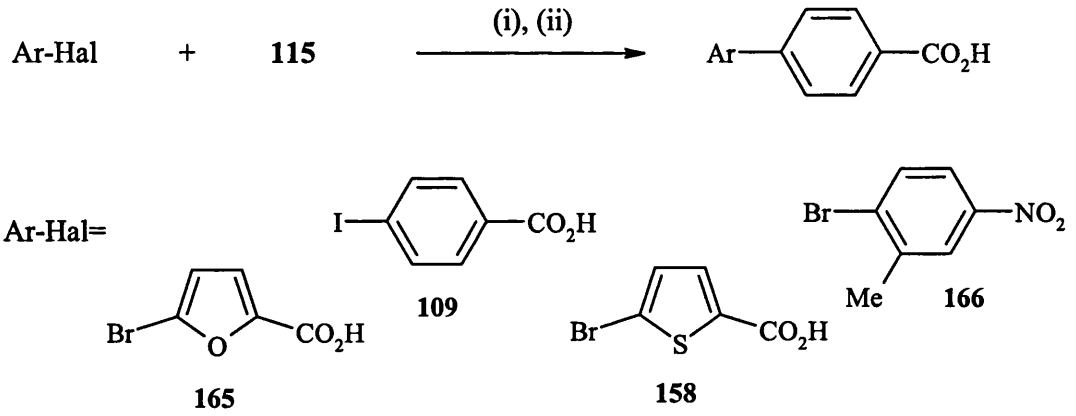
(i)	Palladium content of the aqueous media (%)
1 extraction with Et_2O	0.83
2 extractions with Et_2O	0.14
sp1	< 0.03
sp2	< 0.003

- Table 19 -

These interesting results showed that the sponge beads were able to remove a large amount of the palladium contained in the aqueous mixture. Between the two prepared sponge beads, **sp2** has shown to be more effiecient, as the palladium leaching observed was more than ten times lower than with **sp1**. Besides, in the same conditions the method using the extraction with diethyl ether has only lowered the palladium leaching to a minimum of 0.14%, which is about fifty times higher than the one observed with **sp2**. It

was then important to examine whether the same results would be obtained when these methods are used as a work-up after reactions.

A series of reactions was then carried out to examine the potential of the sponge beads to remove the palladium after reaction. Although the syntheses of compounds **120, 124, 127** and **129** without the supported $Pd(PPh_3)_4$ on the reverse phase catalyst were not really efficient, as low conversions were observed (0 - 50%, see section **2.3.2.5**), they should be acceptable models. The reagents were refluxed for three hours under the conditions described in Scheme 51.



(i): 3 mol% $Pd(PPh_3)_4$, H_2O, 3 h, reflux, N_2; (ii): sponge beads, stirring, r.t., 10 min

- Scheme 51 -

At the end of the reaction, half of the solution was treated with the sponge beads, **sp1** or **sp2** (ratio 1:10 with respect to mass of the catalyst), and the other half extracted twice with diethyl ether. The products were then isolated after treatment with HCl and their palladium levels analysed. These preliminary results are summarised in Table 20. The conversions for all the reactions were low, less than 50%.

Substrate	Palladium leaching (%)		
	sp1	2 extractions with Et_2O	**sp2**
165	< 0.03	0.56 – 3.75	0.06
109	0.12	0.50 – 1.37	0.06
166	[a]	0.19	-
158	-	0.87	< 0.06

[a] No product was isolated.

- Table 20 -

For example, the cross coupling of 5-bromo-2-furoic acid **165** with 4~carboxyphenylboronic acid **115** was carried out in water in the presence of 3 mol% of $Pd(PPh_3)_4$. The sponge beads were added into the mixture at the end of the reaction, and the palladium content was then detected on the isolated solid. It gave less than 0.03% for **sp1** and 0.06% for **sp2**, while the extraction method gave higher palladium leaching levels between 0.56 and 3.75%, Table 20. Also, when the product resulting in the coupling of 4-iodobenzoic acid **109** with 4-carboxyphenylboronic acid **115** was isolated after extraction with diethyl ether, the palladium levels found were lower than the previous one but was still high, from 0.50 to 1.37%. However once again the sponge bead technique gave lower palladium levels than the extraction method, 0.12% for **sp1** and two times less for **sp2** (0.06%). The two methods were also compared for the coupling of 2~bromo-5-nitrotoluene **166** with **115**, but this time only **sp1** was used. The extraction method gave 0.19% of palladium leaching. Surprisingly, after stirring in the sponge beads into the solution, no product precipitated. Finally, the last results were obtained for the coupling of 5-bromo-2-thiophene carboxylic acid **158** with **115**. This time **sp2** was the sponge beads used for removing the palladium and less than 0.06% of metal leaching were observed in the final solid, while 0.87% was found when the solution was extracted with diethyl ether.

2.3.2.6.3 Conclusion

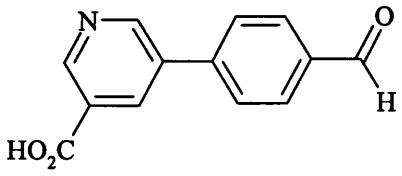
In summary, the technique of sponge beads has proven to be of great potential in the removal of palladium from a reaction mixture or just from a mixture of $Pd(PPh_3)_4$ and water. When the sponge beads **sp2** were used as a work-up method, palladium leaching levels equal or below to 0.06% of the maximum amount of metal that can leach were observed. The sponge beads **sp2** has in general shown a greater efficiency than **sp1**. For the particular example of the coupling of the nitro compound **166**, the sponge beads **sp1** seemed to have also trapped the reagent. This highlights the fact that without the presence of triphenylphosphine on the beads, **sp1** may not be a selective palladium sponge bead and therefore would absorb randomly any organic molecule.

2.3.2.7 Scale up

2.3.2.7.1 Introduction

The success of a heterogeneous catalyst depends on the reproductibility of the reaction, the practicability of the procedure, the possibility of recycling the catalyst, which would decrease the cost, and the low metal leaching observed in the products. When these criteria are fulfilled, industrial application might be a possible option.

So far, the majority of the reactions carried out with the reverse phase catalyst have been performed on a small scale, typically 0.50 mmol and in general the yields observed were good and the catalyst could be recycled at least once. Among all the molecules synthesised using of the reverse phase catalyst, compound **154** has attracted much attention, Figure 18.



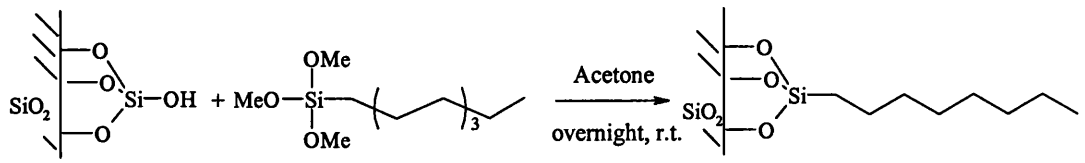
154

- Figure 18 -

This compound was interesting as it contains in the same molecule a carboxylic group, an aldehyde moiety and a pyridine ring. The initial trials attempted by Maybridge plc to synthesise product **154** using a traditional Suzuki cross coupling reaction in organic media, in the presence of the catalyst $Pd(OAc)_2$ with tri-*o*tolylphosphine as added ligand, did not give much success. The product was isolated after purification with a yield of only 28%. However when the reverse phase catalyst was used, the isolated yield rose to 68% of yield without any further purification, as previously reported in section **2.3.2.2.**

2.3.2.7.2 Preparation of the catalyst on large scale

The scaling up of this reaction has then been investigated on an amount of '10 g' for the organohalide **167**. A larger scale for the preparation of the catalyst was also carried out, as shown in Scheme 52.

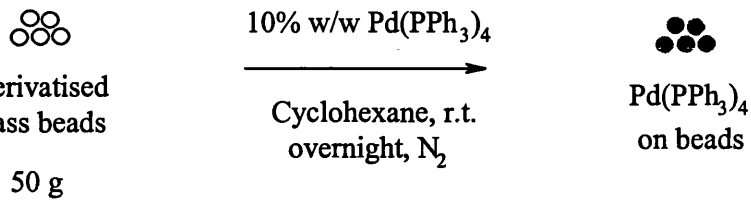


Davisil 500 Å
50 g

112
41.5 mL

- Scheme 52 -

An excess of octyltrimethoxysilane **112** was added to 50 g of Davisil 500 Å and the mixture stirred overnight at room temperature. The derivatised glass beads were collected as previously reported as a white powder. The conversion of 50 g of derivatised glass beads into the active catalyst was also carried out without any difficulties, Scheme 53.

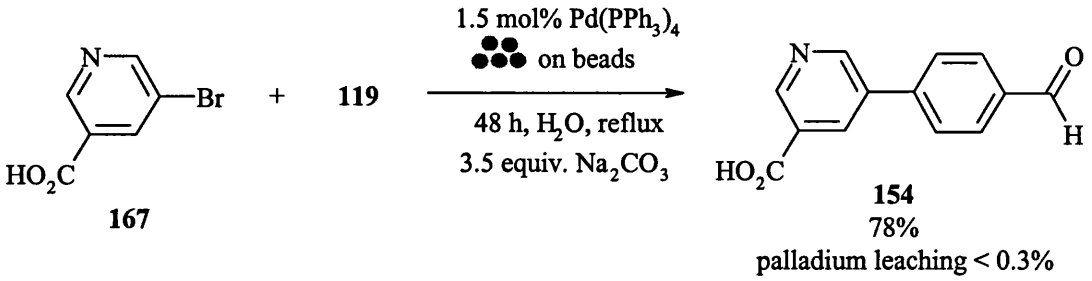


- Scheme 53 -

$Pd(PPh_3)_4$ was added to the mixture of the derivatised glass beads in cyclohexane and stirred overnight. The catalyst was then collected as a grey brown powder after drying under high vacuum for a few hours.

2.3.2.7.3 Synthesis of compound 154

The reaction on a larger scale was then attempted, as shown in Scheme 54. The coupling of 5-bromonicotinic acid **167** with 4-formylphenylboronic acid **119** was carried out in water, in the presence of 1.5 mol% of the reverse phase catalyst and 3.5 equivalents of Na_2CO_3, as described in section **2.3.2.2**. The only change made was the reaction time. Some preliminary syntheses of compound **154** on a scale of 1 g of organohalide showed that more time was needed to complete the reaction. Therefore the mixture was refluxed for 48 hours, and once the reaction was cooled the work up was carried out identically as done on smaller scales.



- Scheme 54 -

On this large scale the separation of the catalyst was not carried out by centrifugation, but by carefully pouring away the aqueous solution. Compound **154** was then isolated in good yield (78%), as a bright yellow solid after extraction with diethyl ether and acidification with concentrated HCl. The palladium leaching level observed in the product was below 0.3%.

In conclusion, the scale up for the preparation of the supported catalyst and the synthesis of compound **154** were achieved without any difficulties. The yield obtained for the scale up was even better (78%) than on the small scale (68%). The results of this scale up also showed that the catalyst is as efficient on small or large scale for the synthesis of **154**. It was also interesting to synthesise compound **154** since it would be a new molecule available if commercialised. The main objective of this scaling up was then to be able to have enough of the product for its commercialisation by Maybridge plc. A further scale up was carried out 'in house' at Maybridge plc, where the previous quantities were doubled (20 g scale reaction). The reaction was carried out and compound **154** was isolated in good yield (62%) with a purity of 97% from HPLC. Molecule **154** (MO 00737) is now available from Maybridge plc.

The use of the reverse phase glass beads holds many advantages and in addition to its reactivity, the fact that the reaction is completely carried out in water is a great advantage in industry as it is environmentally friendly. The process towards the reverse phase catalyst as an efficient industrial heterogeneous catalyst is only at its beginning and more investigation is required for large scale.

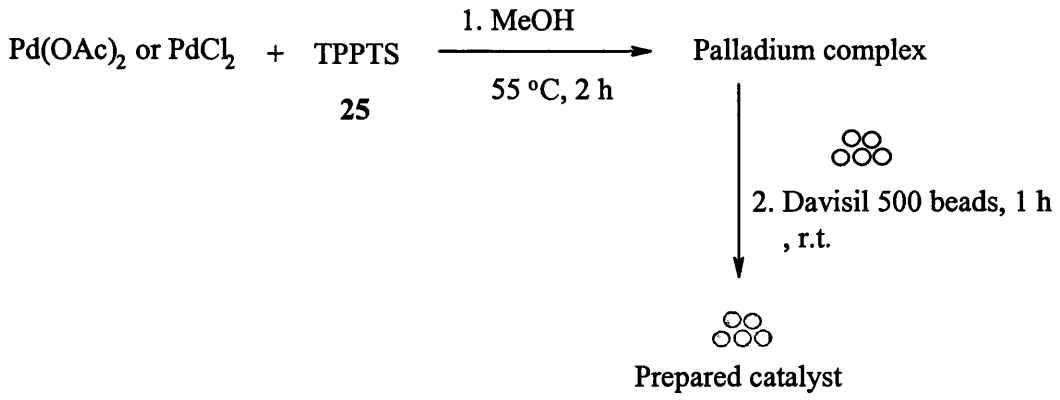
2.3.3 Normal Phase Catalysis[105]

2.3.3.1 Introduction

In the previous sections, the glass bead technology has been exclusively applied to the Suzuki cross coupling in aqueous media using the reverse phase catalyst. At this stage only a few examples reporting the use of the normal phase catalyst for the Suzuki reaction have been investigated within the group. It was then interesting to try to extend the scope of the reaction using the normal phase catalyst. Between the two different types of supported catalyst previously reported in section **2.1.4.3**, the catalyst without ethylene glycol has shown a better efficiency for the Suzuki reaction. Therefore the preparation of this normal phase catalyst was carried out, still using Davisil 500 Å as solid support.

2.3.3.2 Preparation of the catalysts

The preparation of two normal phase catalysts was then carried out using either $PdCl_2$ or $Pd(AcO)_2$ as the palladium source and TPPTS **25** as the water-soluble ligand, following the procedure previously reported within the group, as shown in Scheme 55.

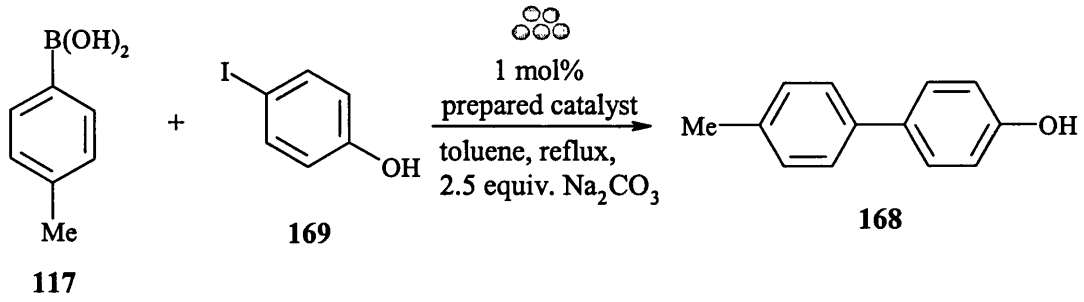


- Scheme 55 -

The palladium catalysts were first preformed *in situ* by mixing one equivalent of $PdCl_2$ or $Pd(OAc)_2$ with two equivalents of TPPTS **25** in methanol and the reaction mixture was stirred at 55 °C for two hours. The silica solid support, Davisil 500 Å, was then added to the solution. The respective normal phase catalysts containing either $PdCl_2$ or $Pd(OAc)_2$ were then collected as two fine powders after removal of the solvent and were simply used by addition to the reaction mixture.

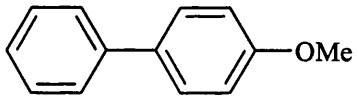
2.3.3.3 Reactivity

The reactivity of the normal phase catalyst was first examined for the Suzuki cross coupling reaction producing a simple biphenyl **168**. In this reaction both normal phase catalysts, with $PdCl_2$ or $Pd(OAc)_2$, were used and therefore their relative reactivity could be compared.



- Scheme 56 -

The Suzuki cross coupling of 4-iodophenol **169** with 4-methylbenzeneboronic acid was carried out in toluene, in the presence of 1 mol% of the prepared catalyst. An aqueous solution of Na_2CO_3 was added and the reaction was refluxed for more than 72 hours, Scheme 56. Unfortunately whatever the catalysts used, no product was synthesised. The synthesis of another molecule, **170**, has also been investigated. The reaction was performed in the same conditions as described in Scheme 56, but once again after more than 24 hours of reaction no product was formed.



170

- Figure 19 -

2.3.3.4 Conclusion

In summary, only two reactions were examined. Neither the supported catalyst preformed from $PdCl_2$ nor $Pd(OAc)_2$ seemed to be efficient for the Suzuki cross coupling in these conditions. Although the results did not confirm the efficiency of the normal phase catalyst as previously reported, more reactions should be investigated.

2.3.4 Ultrasound chemistry

2.3.4.1 Introduction

The ultrasound chemistry or sonochemistry is not really a new subject; the first papers reporting the use of this technique were published in the late 1940's, where it was mainly applied to the polymer chemistry and in some chemical processes.[142,143] In the last decades, the sonochemistry has been given much attention, due to the more general availability of ultrasonic equipment and particularly with the wide spreading of ultrasonic cleaning bath in metallurgic and chemical laboratories. The high efficiency of these ultrasonic baths to clean the glassware and especially to disperse immiscible organic solvents in aqueous detergents have attracted lot of interest and their use to enhance chemical reactivity was then rapidly considered. Fry *et al* have reported one of the first synthesis using ultrasound to promote the reduction of α,α'-dibromoketones into a mixture of α-acetoxyketones.[144] The reaction was performed by dissolving the dibromoketone in acetic acid and by dispersing a small amount of mercury in the solution by means of an ultrasonic cleaning bath for one to four days. The products were formed in moderate to good yields (35 to 80%).

Since this publication, the interest in the application of ultrasound to chemical synthesis has started to grow and applications in biology and biochemistry were also observed. A number of reviews about the chemical applications of ultrasound have been published in last two decades.[145-147]

There are two different types of ultrasound that are commonly used. The first one called *high frequency ultrasound* has a frequency ranged from 2 to 10 MHz, and is generally used in area such as medical scanning. The second one is called *power ultrasound* and has a frequency ranged between 20 and 100 kHz, it is used for cleaning bath and to affect the

chemical reactivity by providing a form of energy which is different from the one normally observed by the means of heat, light or pressure. In organic chemistry most reactions are carried out in solution and the effects of ultrasound in such cases are summarised in terms of three different reactions types, as discussed below.

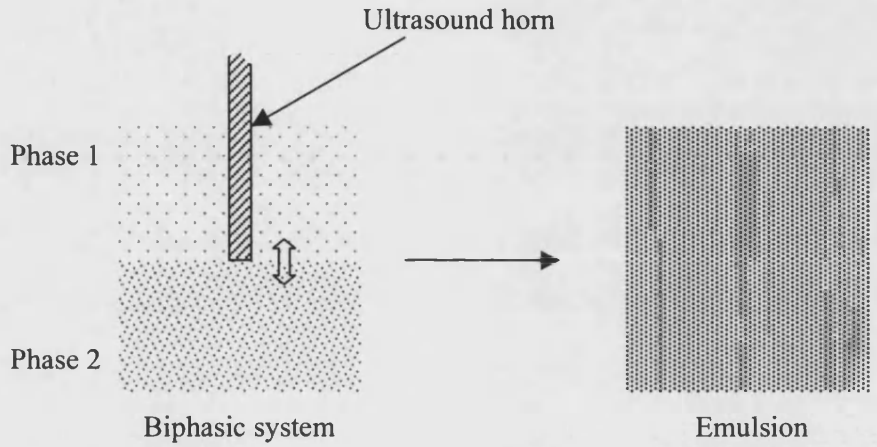
How does the ultrasound chemistry work?

Power ultrasound produces its effects *via* cavitation bubbles. These bubbles are generated during the rarefaction cycle of the wave when the liquid structure is literally torn apart to form microbubbles, which then collapse in the compression cycle. It has been reported that remarkable high pressure and high temperature are generated on collapse of these bubbles.[148]

The first reaction type involves metal surfaces or powders. Although in these cases the way the ultrasound works has not been clearly defined, it is believed that sonication cleans the surface of a metal and therefore makes it more reactive by exposing clean or reactive surface to the reagents and by increasing the effective surface area available for reaction. Indeed dirty surfaces can inhibit a chemical reaction. In some respects, sonication serves a similar purpose than the corresponding chemical techniques. However in some cases, it has been shown that alone the cleaning effect is not sufficient to explain the enhancement of the reactivity and it is believed that there is a sweeping effect. It is thought that sonication serves to sweep from the metal surface products or reactive intermediates, thus constantly presenting renewed clean surface for reaction. The sweeping effect would not be so effective under normal mechanical agitation.

The second reaction type involves emulsion reactions. The technique of ultrasound is known to generate extremely fine emulsions from mixtures of immiscible liquids

(biphasic systems). As shown in Figure 20, the ultrasound horn is placed at the interface of phase 1 and 2, which are immiscible and the vibrations then create the phenomenon of cavitation bubbles that gives the emulsion. And after enough time the emulsion gives back the two separate phases.



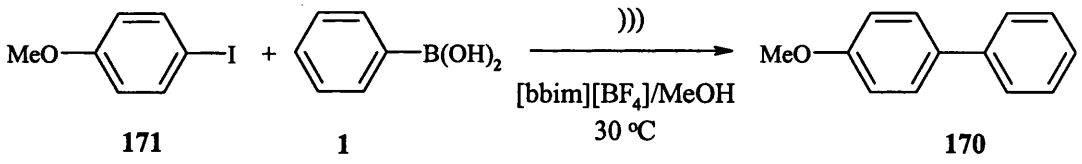
- Figure 20 -

In such emulsions there is a dramatic increase in the interfacial contact area between the liquids *i.e.* an increase in the region over which any reaction between species dissolved in the liquids can take place. These properties can allow the use of ultrasound instead of phase transfer agents in most cases, however it has been found that a combination of both can be more efficient.

The third reaction type involves homogeneous reactions. The fact that reactions promoted by ultrasound also work effectively in a single-phase shows that the enhancement of the reactions can not be only attributed to the mechanical results of cavitational bubble collapse. In fact, for example it was discovered that light could be emitted when water is

sonicated (sonoluminescence) or that the sonication can fragment liquid alkanes or accelerate their solvolysis in aqueous alcoholic solvents.

In summary, some of the beneficial influences such as acceleration of the reaction or less drastic conditions can be achieved with the ultrasound chemistry. Several synthetic organic applications have been reported using this chemistry, however there are only a few examples for palladium catalysed cross coupling reactions. For example recently, Rajagopal *et al* have reported the ultrasound promoted Suzuki cross coupling reactions in ionic liquid at room temperature.[44] An illustration is the cross coupling of 4~methoxyiodobenzene **171** with phenyl boronic acid **1** in presence of $Pd(OAc)_2$, which was carried out in the ionic liquid [bbim][BF_4] with methanol as co-solvent. The reaction was performed in a thermostated ultrasonic cleaning bath. After 20 minutes of reaction at room temperature compound **170** was isolated in good yield (93%), Scheme 57.



171 **1** **170**

- Scheme 57 -

While the ionic liquid was recycled several times, the use of ultrasound on $Pd(OAc)_2$ yielded to the formation of black palladium, which then prevents the recycling of the catalyst. The coupling of various chlorocompounds was also examined and showed moderate conversion (42 to 52%).

Although the use of ultrasonic cleaning bath is practical and mostly accessible, several factors such as the control of the temperature is not always possible and because cleaning baths do not operate at the same frequency it can be difficult to reproduce results reported in the literature.

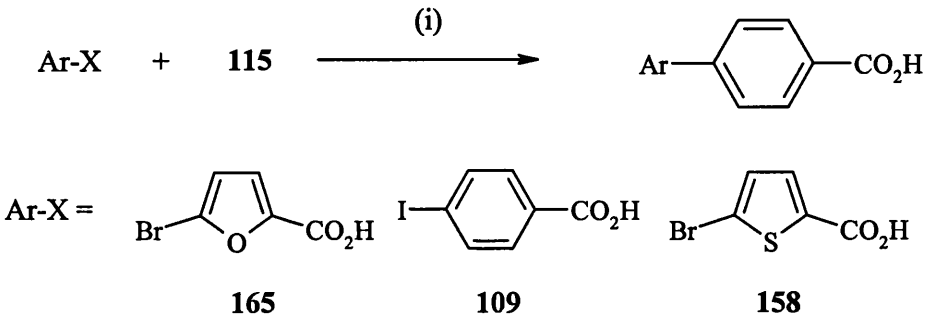
2.3.4.2 Aims

As previously described, the use of ultrasound in organic chemistry can considerably accelerate a reaction. Only one example of Suzuki cross coupling has been reported and ionic liquid and ligandless catalyst were mainly used, scheme 57.

Although biphasic systems have proven their efficiency for the catalytic synthesis, the insolubility of the reagents in one phase can be a problem. A solution can be provided by the use of ultrasound. In our study, the focus was made on the examination of a biphasic system where all the reagents will be solubilised in water and the catalyst will reside in an organic phase. The cross coupling will then be promoted by ultrasound through the formation of a fine emulsion, which increase significantly the contact area between the two phases. Since the use of sonication can increase the temperature, it was important to have an idea of how much heat was produced by this process. The temperature was then monitored throughout the reactions. In addition the reactions were also reproduced, but this time they were promoted by heating and under a strong agitation. It would then be eventually possible to discuss and compare whether the ultrasound or just the heating is responsible for the cross coupling reaction.

2.3.4.3 Reactivity

The syntheses of three compounds **120, 127** and **129,** which have worked efficiently with the reverse phase catalyst, were chosen for this study, Scheme 58. For each one of them the reaction has been performed with heating and with ultrasound.



165 **109** **158**

(i): water/toluene (1:1), $Pd(PPh_3)_4$, N_2, Na_2CO_3,))) or 110 °C

- Scheme 58 -

While toluene is a classical solvent for the Suzuki cross coupling, it was important to be sure that under sonication a good emulsion was formed from the combination of toluene and water. The sonication of a mixture of water/toluene (1:1) gave a good emulsion, thus toluene was chosen as the organic co-solvent.

All the presented results are preliminary as the reactions were carried out once, only for a few substrates, and were not optimised. To avoid an over heating of the reaction it was decided to use the ultrasound over two hours with a 50% duty cycle, this means that the irradiation will be produced only over 30 seconds per minute. In summary, there will be a total of one hour of ultrasound. The reaction time was two hours for all the reactions.

For example, the Suzuki cross coupling of 5-bromo-2-furoic acid **165** with 4~carboxyphenylboronic acid **115** was carried out in a 1:1 mixture of water/toluene in presence of 3 mol% of $Pd(PPh_3)_4$, 4.5 equivalents of Na_2CO_3 and under nitrogen. The

temperature increased during the sonication from 25 °C to 71 °C, Table 21. After the reaction, the emulsion was allowed to rest to give back the two separate phases. The product **127** was then isolated after work up, with a conversion of 88%, and 12% of self-coupling product was also observed, Table 21.

Product	Δ or)))	Product conversion (%)		Temperature (°C)
		Self coupling	Cross coupling	
127	)))	12	88	25 – 71
	Δ	0	0	110
120	)))	0	100	23 – 71
	Δ	0	100	110
129	)))	21	79	25 – 73
	Δ	11	89	110

- Table 21 -

The same cross coupling was then carried out by heating the water/toluene mixture at 110 °C under strong stirring. After two hours of reaction no product was formed at all, only the starting materials were recovered. These results showed that for this coupling, since the heating does not give the coupling product at all, the use of ultrasound is effective in promoting the reaction.

The coupling of 4-iodophenyl carboxylic acid **109** with 4-carboxyphenylboronic acid **115** was also examined. After two hours of reaction promoted by ultrasound, the temperature increased in a similar way as previously reported, from 23 to 71 °C. A complete conversion was observed for the formation of product **120** and no self-coupling product was observed as no starting materials were recovered. The same conversions were

obtained for the reaction promoted by heat at 110 °C and no self-coupling product was formed.

Finally the coupling of 5-bromo-2-thiophene carboxylic acid with 4-carboxyphenylboronic acid **115** was carried out under both conditions. The reaction promoted by ultrasound gave the product **129** with a conversion of 79% and 21% of conversion were observed for the self-coupling product. During the reaction the temperature increased to a maximum of 73 °C. It was interesting to note that less self-coupling product (11% of conversion) was formed when the reaction mixture was heated leading to a conversion of 89% for the cross coupling product **129**. For the synthesis of products **120** the comparison between ultrasound and heating showed similar reactivity.

The uses of biphasic systems for catalytic reactions usually allow the recycling of the catalyst at the end of the reaction. For all the reactions carried out with ultrasound, it was observed that the catalyst started to get black after only 20 minutes, which also means that the reactions were probably over after only 20 minutes.

2.3.4.4 Conclusion

The general conversions observed for the ultrasound promoted Suzuki cross coupling of various reagents in presence of $Pd(PPh_3)_4$ in a mixture of water and toluene were high, from 79% to 100%. Only the synthesis of compound **127** gave a better result than the reaction promoted by heating. On the other hand, only the synthesis of compound **127** when carried out with heating did not work. The palladium leaching levels in all the products were low, below 1%, except for compound **129** where a higher palladium leaching of 31% was detected (the isolated product was dark green).

As general observations, although the ultrasound was on a 50% cycle duty the temperature rose slightly above 70 °C during the reaction and this could have an influence. Also, no emulsion was observed when a strong stirring was set for all the reactions carried out without ultrasound.

Conclusion And Future Work

3.1 Reactivity

The glass bead technology has been first applied effectively to a variety of catalytic reactions, and more recently to various palladium-catalysed reactions such as Heck or allylic substitution, but not much attention has been given to the Suzuki reaction. The use of a reverse phase catalyst has then been investigated for the Suzuki cross coupling reaction of various organohalides and boronic acids in aqueous media. The reverse phase catalyst allowed then the use of the conventional catalyst $Pd(PPh_3)_4$. The supported catalyst was easily prepared from the loading of $Pd(PPh_3)_4$ onto the derivatised glass beads and was handled under a normal atmosphere.

In general the cross coupling of bromo- and iodoreagents with various boronic acids gave similar results, but in the presence of both halides in the same molecule only the C-I bond has reacted for the synthesis of compound **149**. The cross coupling of chlororeagents was also investigated, but the conversions observed for the cross coupling of 4-chlorophenyl carboxylic acid with boronic acids **115** and **116** in the presence of the reverse phase catalyst were low, below 7%. Palladium catalysts such as palladacycles have proven to be powerful tools for the Suzuki cross coupling of a broad range of reagents, including chlororeagents. The heterogenisation of these catalysts without any further transformations by directly loading the catalyst onto the derivatised glass beads could give some interesting results for the Suzuki cross coupling in aqueous media.

The reverse phase catalyst has proven to be an efficient catalyst for the cross coupling of aryl halides with arylboronic acids in aqueous media. Although most reactions were in average refluxed for two or three hours, it was probably not a requirement as it was observed for the synthesis of compounds **120** and **127** that a reaction time of less than ten

minutes was sufficient to complete the reactions. The investigation of the cross coupling of alkenylhalides with arylboronic acid **115** was also considered, but the reactions were unsuccessful. The use of stronger base than Na_2CO_3, such as NaOH, may be considered to increase the cross coupling product.

Among the eight boronic acids tested for the Suzuki reaction in the presence of the reverse phase catalyst, only the cross coupling of boronic acid **115** gave some self coupling product. In general the self-coupling product was formed in low conversion (10%).

3.2 Palladium leaching levels

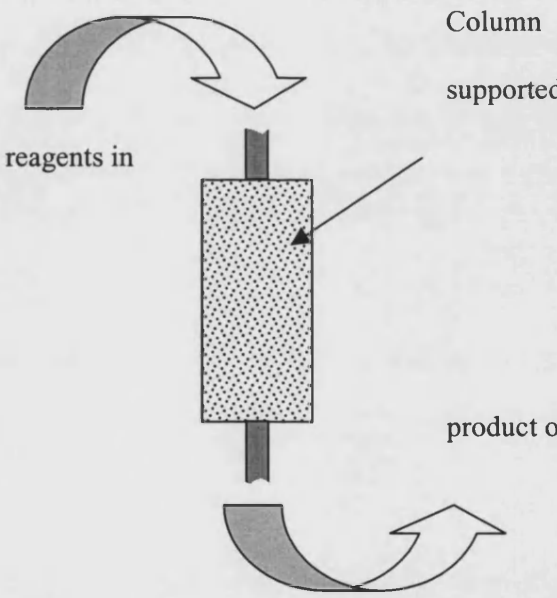
For most of the coupled products synthesised using the reverse phase catalyst, the palladium leaching levels were low, in general around 0.1%. The only exception were observed when either the reagents or the boronic acid were less water soluble and / or containing some groups that would be capable to act like a ligand with the palladium and to draw it into the phase containing the product.

3.3 Recycling

The recycling of the catalyst has been investigated for the Suzuki cross coupling. In conclusion, the reverse phase catalyst can be used twice, but the third use was unsuccessful. One reason could be attributed to the loss of triphenylphosphine due to the presence of water. This problem could be solved by using a non-phosphine ligand, avoiding then the formation of the phosphine oxide. Also, it would be interesting to be able to draw the palladium from the solid support for two reasons. The first one, to have an idea of the 'state' of the palladium catalyst after reactions, and the second reason, to be

able to recycle the solid support. Indeed, if the unreacted or inactive catalyst is removed from the solid support, this one can then be recycled and loaded with fresh $Pd(PPh_3)_4$.

In a long term, the elaboration of a fully recyclable catalyst would be of interest for the industry. The use of the supported catalyst in a continuous flow reaction would be a good application, as described in Figure 21. In this system the reagents, in water for example, are introduced into a column containing the reverse phase catalyst in the same solvent. The reaction occurred throughout the column to give the product at the other end and continuously more reagents can be introduced into the column.



- Figure 21 -

3.4 Comparison of the supported catalyst with $Pd(PPh_3)_4$

Although this study was only realised on a few examples, it showed that the supported catalyst was more efficient in the Suzuki cross coupling reaction than the unsupported

$Pd(PPh_3)_4$ placed in the same conditions. The use of glass beads increases the surface of contacts between the reagents and catalyst. Also, the self-coupling reaction seems to always proceed in the first 30 minutes of the reactions, when it occurred.

3.5 Scale up

The scaling up process for the synthesis of compound **154** has been carried out without any difficulties and **154** is now commercially available from Maybridge plc.

3.6 Sponge beads, ultrasound chemistry and normal phase catalysis

In summary, the sponge beads method was more efficient than just the extraction of the reaction mixture with Et_2O. The sponge beads with triphenylphosphine, **sp2**, was more effective than **sp1** (without added ligands), a low palladium leaching level below 0.06% was observed when used as work up. Once again the recycling of the sponge beads by the removal of the catalyst would be interesting.

Finally, more investigations and optimisation of the reaction conditions need to be carried out for the Suzuki reaction promoted by ultrasound and the reactions in the presence of the normal phase catalyst.

3.7 Summary

The glass bead technology holds many advantages and the use of a reverse phase catalyst, which allows the use of water as solvent, is economically and ecologically friendly. In general, the application of this technology to the Suzuki cross coupling has shown it efficiency.

Experimental

4.1 General procedures

Commercially available solvents and reagents were obtained from Sigma-Aldrich Company Ltd, and Fisher Scientific Ltd and were used throughout without further purification. Deionised water was used. Dichloromethane was distilled from calcium hydride and tetrahydrofuran was distilled from sodium wire. Solvents and reagents were deoxygenated where necessary by purging with nitrogen. Petrol refers to the fraction of petroleum ether boiling in the range of 40 - 60 °C.

Davisil 500 Å 663 XWP (particle size: 35 - 70 μm, Surface Area: 75 - 85 m^2/g, Pore size: 500 Å) was purchased from Supelco and Sigma-Aldrich Company Ltd.

Analytical thin layer chromatography was performed on pre-coated aluminium-backed silica gel (Merck Kiesegel 60 F_{254}) plates and visualised under ultra-violet light (at 254 nm or 365 nm) and / or by staining with potassium permanganate and vanillin followed by heating. Column chromatography was carried out using Merck Kiesegel 60 H silica gel.

Bath University

Melting points were measured on a Büchi 535 instrument and are uncorrected. Infrared spectra were measured in the range of 4000 – 600 cm^{-1} using a Perkin-Elmer 1600 series FT-IR spectrophotometer, with internal calibration. Spectra were recorded as potassium bromide disks. Electron Impact (EI), Chemical Ionisation (CI) and Fast Atom Bombardment (FAB) mass spectra were obtained using a Fisons VG Autospec.

^{1}H and ^{13}C NMR spectra were recorded on either a JEOL EX-400 or a Bruker 300. Chemical shifts (δ) are expressed in parts per million (ppm), and are relative to an internal reference of residual protic solvent. The general multiplicities of the spectroscopic data are presented in the following manner: singlet (s), apparent singlet (app s), broad singlet (br s), doublet (d), apparent doublet (app d), doublet of doublets (dd), triplet (t), apparent triplet of doublets (app td), and multiplet (m). Coupling constants (J) are expressed in Hz. The notation for the proton of thiophene rings has been simplified to Thio-H, for furan rings to Fur-H, for pyridine rings to Pyr-H, for the nitrotoluene ring NO_2-Ar and for all other aryl rings to Ar-H. The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however, the characteristic features of AA'BB' system were sometimes observed in the NMR spectra.

Elemental analyses were performed using an Exeter analytical Inc CE-440 Elemental Analyser.

Palladium analyses were performed using atomic absorption (AA) on a Varian AA-275 series spectrometer. A hollow cathode lamp provided the light source, and was purchased from S+S Juniper Ltd. A palladium atomic absorption standard solution (1000 $\mu g/cm^3$ in 5 wt% hydrochloric acid) was purchased from Sigma-Aldrich Company Ltd and diluted as necessary to provide a range of calibration standards.

The source of ultrasound source was a Sonics and Materials VC600 horn system operating at 23 ± 1 kHz.

Maybridge plc

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 250. The LC/MS analyses were performed on an Agilent 1100 HPLC comprising quaternary gradient pumps, a thermostated column compartment with two-way column switching valves and a diode array detector, a Gilson 215 autosampler, a Platform LC mass spectrometer, a single-stage quadrupole instrument with electrospray ionisation source.

4.2 CHAPTER 2 experimental

4.2.1 The reverse phase catalysis

Derivatisation of the glass beads[105]

Derivatised
glass beads

To Davisil 500 Å (5.00 g) in absolute acetone (25 mL) was added octyl trimethoxysilane **112** (4.15 mL). The reaction mixture was stirred overnight at room temperature under nitrogen. The derivatised silica was then collected as a fine white powder, after removal of the solvent under reduced pressure. The resulting powder (4.90 g) was then dried under high vacuum.

Loading of $Pd(PPh_3)_4$ onto the derivatised glass beads

$Pd(PPh_3)_4$
on beads

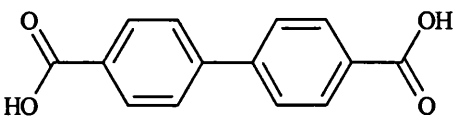
To the derivatised glass beads (500.0 mg) in cyclohexane (5 mL) was added under nitrogen a solution of $Pd(PPh_3)_4$ (50.0 mg, 0.04 mmol) in cyclohexane (5 mL). The reaction mixture was stirred at room temperature overnight under nitrogen. The solvent was then removed under reduced pressure to yield a fine grey brown powder (498.0 mg), which was dried under high vacuum.

Synthesis of palladium tetrakis(triphenylphosphine)[127]

$Pd(PPh_3)_4$

A mixture of palladium dichloride (2.00 g, 11.00 mmol), triphenylphosphine (14.78 g, 56.00 mmol), and dimethyl sulfoxide (120 mL) was heated with stirring until complete solution occured (~140 °C). The solution was then rapidly stirred for approximately 15 min at room temperature. Hydrazine hydrate (2.20 g, 44.00 mmol) was then rapidly added over 1 min. A vigorous reaction took place with evolution of nitrogen. The dark solution was then immediately cooled with a water bath and precipitation began to occur at 125 °C. At that point the reaction mixture was allowed to cool without external cooling. After the mixture reached room temperature, it was filtered under nitrogen on a sintered-glass funnel. The solid was washed successively with EtOH and Et_2O under nitrogen. The product was then dried overnight under high vacuum. The catalyst was obtained as a yellow powder (12.00 g, 10.34 mmol, 94%). mp 114 °C (lit.,[127] 116 °C).

Typical procedure A, for using the derivatised glass beads in aqueous media: Synthesis of [1,1'-biphenyl]-4,4'-dicarboxylic acid, 120[149]



To a mixture of 4-iodophenylcarboxylic acid **109** (124.0 mg, 0.50 mmol) and supported catalyst (174.0 mg, 3 mol%) in water (5 mL), was added Na_2CO_3 (250 μL, 0.50 mmol, 2M). Then a solution of 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol) and

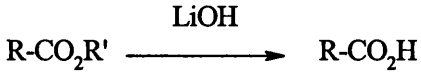
Na_2CO_3 (275 μL, 0.55 mmol, 2M) in water (5 mL) was added to the mixture. Finally, 2.5 equivalents of Na_2CO_3 was added (625 μL, 1.25 mmol, 2M) and the solution was heated at reflux until completion of the reaction (1.5 h). The supported catalyst was separated from the solution by centrifugation or decantation, the remaining solution was then extracted with Et_2O (2 × 10 mL), and acidified with HCl (concentrated 37% or 2N) to give compound **120** (104.2 mg, 0.43 mmol, 86%) as a colourless solid, which was isolated after filtration and drying under vacuum. mp >300 °C (lit.,[149] >350 °C); δ_H (300 MHz; d_6-DMSO): 13.00 (2H, br s, CO_2H), 8.35 (4H, d, J = 8.0, Ar-H), 7.85 (4H, d, J = 8.0, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 166.3 (CO_2H), 142.3 (C), 129.6 (C), 129.3 (CH), 126.4 (CH), *m/z* (CI) 242.9 (9%, MH^+), 122.9 (100%, $C_6H_4CO_2H_2^+$)

Typical procedure for esterification, method B[131]

$$R\text{-}CO_2H \xrightarrow{EtOH} R\text{-}CO_2Et$$

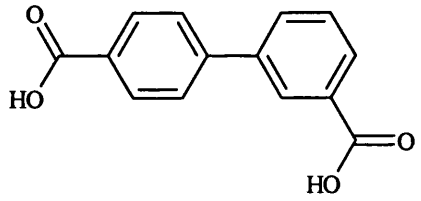
A solution of carboxylic acid (1.00 mmol), N,N-dicyclohexylcarbodiimide (22.7 mg, 1.10 mmol), ethanol (51.0 mg, 1.10 mmol) and 4-pyrrolidinopyridine **141** (15.0 mg, 0.10 mmol) in dichloromethane (3 mL) was allowed to stand at room temperature overnight. The *N,N*-dicyclohexyl urea was filtered and the filtrate washed successively with water (3 × 5 mL), 5% acetic acid solution (3 × 5 mL) and water (3 × 5 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petrol then petrol/ethyl acetate 90/10), to give the corresponding ester.

Typical procedure for saponification, method C[132]



To a solution of the ester (0.12 mmol) in MeOH/H_2O (3:1, 4 mL) at 5 °C was added LiOH.H_2O (26.0 mg, 0.62 mmol), and the reaction mixture stirred overnight. MeOH was then removed under reduced pressure and deionised water (3 mL) was added to the remaining aqueous solution, which was then acidified with concentrated HCl (0.5-1mL, 37%) to give after filtration and drying under high vacuum the corresponding carboxylic acid as a solid.

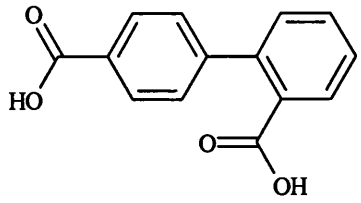
Synthesis of [1,1'-biphenyl]-3,4'-dicarboxylic acid, 121[150]



Following the general procedure A, to a solution of 3-iodophenylcarboxylic acid **172** (62.0 mg, 0.25 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.6 mg, 0.27 mmol), Na_2CO_3 (565 μL, 1.12 mmol, 2M) and the supported catalyst (87.0 mg, 3 mol%). The reaction was then heated at reflux for 1.5 h to yield compound **121** (48.4 mg, 0.20 mmol, 80%) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp >307 °C (lit.,[150] 336-337 °C); δ_H (300 MHz; d_6-DMSO) 13.10 (2H, br s, CO_2H), 8.23 (1H, app s, Ar-H), 8.03 (2H, d, J = 8.3 Ar-H),

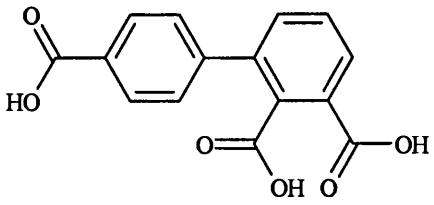
7.97 (2H, app d, J = 7.7, Ar-H), 7.82 (2H, d, J = 8.3, Ar-H), 7.62 (1H, app t, J = 7.7, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 167.4 (CO_2H), 167.4 (CO_2H), 143.6 (C), 139.7 (C), 131.9 (C), 131.7 (CH), 130.4 (C), 130.3 (CH), 129.8 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH); *m/z* (EI) 242.1 (100%, M^+).

Synthesis of [1,1'-biphenyl]-2,4'-dicarboxylic acid, 122[151]



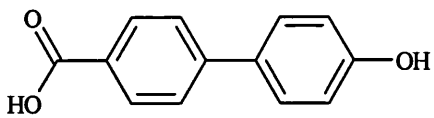
Following the general procedure A, to a solution of 2-iodophenylcarboxylic acid **173** (62.0 mg, 0.25 mmol), in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.6 mg, 0.27 mmol), Na_2CO_3 (565 μL, 1.12 mmol, 2M) and the supported catalyst (87.0 mg, 3 mol%). The reaction was then heated at reflux for 1.5 h to yield compound **122** (38.0 mg, 0.16 mmol, 63%) as a colourless solid after acidification with HCl, filtration and drying under vacuum. ν_{max}(KBr disc)/cm^{-1} 2981 (br, OH), 1703 (C=O), 1683 (C=O); δ_H (300 MHz; d_6-DMSO) 12.95 (2H, br s, CO_2H), 7.95 (2H, d, J = 8.2, Ar-H), 7.78 (1H, dd, J = 1.1, 7.6, Ar-H), 7.60 (1H, app td, J = 7.6, 1.1, Ar-H), 7.51 (1H, app td, J = 7.6, 1.1, Ar-H), 7.43 (2H, d, J = 8.2, Ar-H), 7.39 (1H, dd, J = 7.6, 1.1); δ_C (75.5 MHz; d_6-DMSO) 169.5 (CO_2H), 167.7 (CO_2H), 145.8 (C), 140.8 (CH), 140.7 (C), 132.3 (CH), 131.5 (C), 131.1 (CH), 130.8 (C), 129.8 (CH), 129.6 (CH); *m/z* (EI) 242.1 (15%, M^+), 214.1 (32%, M^+-CO), 77.0 (100%).

Synthesis of [1,1'-biphenyl]-2,3,4'-tricarboxylic acid, 126[152]



Following the general procedure A, to a solution of 4-bromophthalic acid **164** (122.5 mg, 0.50 mmol), in deionised water (10 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1.375 μL, 2.75 mmol, 2M,) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 1.5 h to yield compound **126** (138.7 mg, 0.48 mmol, 97%) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp 295 – 296 °C (lit.,[152] 302-303 °C); δ_H (300 MHz; d_6-DMSO): 13.20 (3H, br s, CO_2H), 8.04 (2H, d, J = 8.3, Ar-H), 8.00-7.75 (3H, m, Ar-H) and 7.87 (2H, d, J = 8.3, Ar-H).; δ_C (75.5 MHz; d_6-DMSO) 168.9 (CO_2H), 168.5 (CO_2H), 167.3 (CO_2H), 142.7 (C), 141.6 (C), 134.5 (C), 132.2 (C), 130.8 (C), 130.42 (CH), 129.8 (CH), 129.3 (CH), 127.5 (CH), 126.9 (CH); *m/z* (CI) 269.0 (100%, MH^+-H_2O).

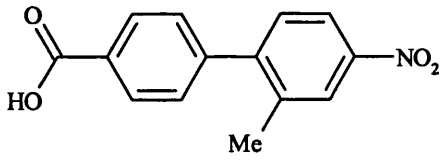
Synthesis of 4'-hydroxy[1,1'-biphenyl]-4-carboxylic acid, 123[153]



Following the general procedure A, to a solution of 4-iodophenol **169** (55.0 mg, 0.25 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (46.6 mg,

0.27 mmol), Na_2CO_3 (562 μL, 1.12 mmol, 2M) and the supported catalyst (87.0 mg, 3 mol%). The reaction was then heated at reflux for 1.5 h to yield compound **123** (138.7 mg, 0.48 mmol, 97%) as a crude solid after acidification with HCl, filtration and drying under vacuum. ν_{max}(KBr disc)/cm^{-1} 3421 (br, OH), 1582 (C=C), 1541 (C=C), 833 (Ar-H), 789 (Ar-H); δ_H (300 MHz; d_6-DMSO) 12.90 (1H, br s, CO_2H), 9.71 (1H, s, OH), 7.95 (2H, d, J = 8.3, Ar-H), 7.69 (2H, d, J = 8.3, Ar-H), 7.57 (2H, d, J = 8.5, Ar-H), 6.86 (2H, d, J = 8.5, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 167.6 (CO_2H), 158.2 (C), 144.7 (C), 130.3 (CH), 128.8 (C), 128.5 (CH), 127.5 (CH), 127.0 (CH), 116.2 (CH); *m/z* (EI) 214.0 (100%, M^+), 197.0 (35%, M^+-OH), 169 (8%, M^+-CO_2H).

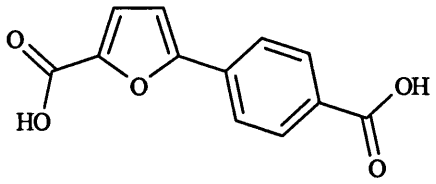
Synthesis of 2'-methyl-4'-nitro[1,1'-biphenyl]-4-carboxylic acid, 124



Following the general procedure A, to a solution of 2-bromo-5-nitrotoluene **166** (108.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M,) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h to yield compound **124** (99.9 mg, 0.40 mmol, 78 %) as a solid after acidification with HCl, filtration and drying under vacuum. The purification was carried out by following procedures B and C, which gave compound **124** as a yellow solid (23.7 mg, 0.09 mmol, 18%). mp 267 °C (decomposition); ν_{max}(KBr disc)/cm^{-1} 2969 (br, OH), 1684 (C=O), 1608 (C=C), 1521 (N=O), 1350 (N^+-O^-), 745 (Ar-H); δ_H (300 MHz; d_6-DMSO) CO_2H not observed, 8.24

(1H, app s, NO_2-Ar-H), 8.14 (1H, d, J = 8.2, NO_2-Ar-H), 8.05 (2H, d, J = 7.8, Ar-H), 7.87 (1H, d, J = 8.2, NO_2-Ar-H), 7.53 (2H, d, J = 7.8, Ar-H), 2.35 (3H, s, CH_3); δ_C (75.5 MHz; d_6-DMSO) 167.8 (CO_2H), 147.9 (C), 144.3 (C), 143.9 (C), 138.2 (C), 131.7 (CH), 131.2 (C), 130.9 (CH), 130.3 (CH), 129.9 (CH), 128.0 (CH), 125.9 (CH), 121.9 (CH), 20.9 (CH_3); *m/z* (EI) 257.1 (11%, M^{+}), 69.1 (100%), Accurate Mass found: M^{+}, 257.0691 $C_{14}H_{11}NO_4$ requires 257.0688.

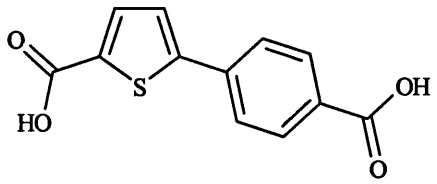
Synthesis of 5-(4-carboxyphenyl)-2-furoic acid, 127



Following the general procedure A, to a solution of 5-bromo-2-furoic acid **165** (47.7 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.6 mg, 0.55 mmol), Na_2CO_3 (1125 μL, 2.25 mmol, 2M,) and the supported catalyst (87.0 mg, 3 mol%). The reaction was then heated at reflux for 1 h to yield compound **127** (53.0 mg, 0.45 mmol, 91%) as a solid after acidification with HCl, filtration and drying under vacuum. The purification was carried out by following procedures B and C, which gave compound **127** as a colourless solid (5.2 mg, 0.02 mmol, 4%). mp 299 – 302 °C; ν_{max}(KBr disc)/cm^{-1} 2884 (br, OH), 1674 (C=O), 1539 (C=C), 1483 (C=C); δ_H (300 MHz; d_6-DMSO) 13.2 (2H, br s, CO_2H), 8.04 (2H, d, J = 8.3, Ar-H), 7.94 (2H, d, J = 8.3, Ar-H), 7.37 (1H, d, J = 3.6, Fur-H), 7.32 (1H, d, J = 3.6, Fur-H); δ_C (75.5 MHz; d_6-DMSO) 167.6 (CO_2H), 160.0 (CO_2H), 155.9 (C), 145.8 (C), 133.5 (C), 131.4 (C), 131.0 (CH), 125.2 (CH), 120.7 (CH), 110.7 (CH); For the ester: *m/z* (EI) 288.1 (100%, M^{+}), 243.1 (58

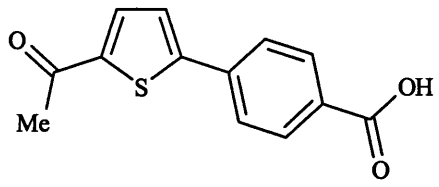
%, M^{+}-OEt), 215.1 (59%, M^{+}-CO_2Et), Accurate Mass found: M^{+}, 288.0998 $C_{16}H_{16}O_5$ requires 288.0998.

Synthesis of 5-(4-carboxyphenyl)-2-thiophenecarboxylic acid, 129



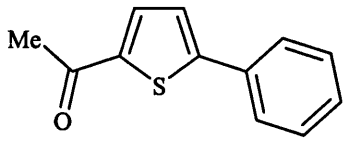
Following the general procedure A, to a solution of 5-bromo-2-thiophene carboxylic acid **158** (102.5 mg, 0.50 mmol) in deionised water (12 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1125 μL, 2.25 mmol, 2M) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h to yield compound **129** (106.0 mg, 0.42 mmol, 85%) as a cream solid after acidification with HCl, filtration and drying under vacuum. mp >307 °C; (Found: C, 52.59; H, 3.16 $C_{12}H_8SO_4$+3/2(H_2O) requires C, 52.36; H, 2.93); ν_{max}(KBr disc)/cm^{-1} 2969 (br, OH), 1683 (C=O), 1681 (C=O), 1605 (C=C), 1511 (C=C); δ_H (300 MHz; d_6-DMSO) CO_2H not observed, 7.98 (2H, d, J = 8.4, Ar-H), 7.86 (2H, d, J = 8.4, Ar-H), 7.85 (1H, d, J = 3.9, Thio-H), 7.50 (1H, d, J = 3.9, Thio-H); δ_C (75.5 MHz; d_6-DMSO) 167.4 (CO_2H), 163.0 (CO_2H), 148.5 (C), 137.0 (C), 134.5 (C), 130.9 (C), 130.6 (CH), 127.4 (CH), 126.2 (CH), 126.1 (CH); *m/z* (CI) 248.9 (39%, MH^{+}), 69.0 (100%); (LC / MS: *m/z* (ES-) 247.0 (5%, M-H), 203.1 (100%), LC 2.66 min (100%, M)).

Synthesis of 4-(5-acetyl-2-thienyl) benzoic acid, 125



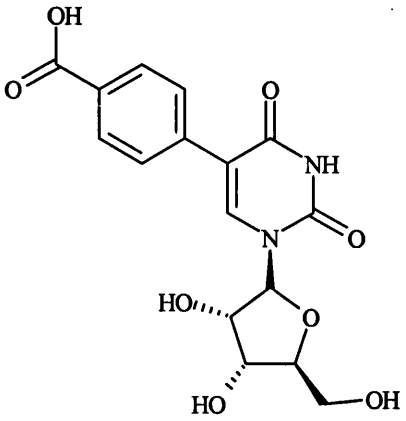
Following the general procedure A, to a solution of 2-acetyl-5-bromothiophene **174** (102.5 mg, 0.50 mmol) in deionised water (12 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M,) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h. When cooling a yellow pale solid precipitated, the solution and the solid were separated by decantation and the mixture was extracted with Et_2O. The remaining aqueous solution containing the solid was acidified with concentrated HCl (37%) and filtered to yield compound **125** (96.0 mg, 0.39 mmol, 78%) as a bright yellow solid after drying under vacuum. mp >307 °C; ν_{max}(KBr disc)/cm^{-1} 3075 (br, OH), 1660 (MeC=O), 1633 (C=O), 1583 (C=C), 1542 (C=C). δ_H (250 MHz; d_6-DMSO) CO_2H not observed, 7.90 (2H, d, *J* = 8.2, Ar-H), 7.76 (2H, d, *J* = 8.2, Ar-H), 7.63 (1H, d, *J* = 3.7, Thio-H), 7.59 (1H, d, *J* = 3.7, Thio-H), 2.58 (3H, s, CH_3); (EI) 245.9 (75%, M^+), 230.9 (100%, M^+-Me), Accurate Mass found: M^+, 246.0359 $C_{13}H_{10}SO_3$ requires 246.0351. (LC / MS: *m/z* (ES+) 245.04 (100%, M+H), (ES-) 247.02 (100%, M-H), LC 2.99 min (100%, M).

Synthesis of 5-acetyl-2-phenylthiophene, 153[154]



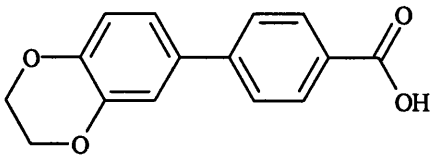
Following the general procedure A, to a solution 2-acetyl-5-bromothiophene **174** (102.5 mg, 0.50 mmol) in deionised water (12 mL) were added phenylboronic acid **1** (67.1 mg, 0.55 mmol), Na_2CO_3 (625μL, 1.25 mmol, 2M) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h. The hot reaction mixture was then filtrated to separate the catalyst from the solution. When cooling a solid precipitated, which was then isolated by filtration. The solid was purified by column chromatography (SiO_2, petrol then petrol/ethyl acetate 90/10) to yield compound **153** (53.5 mg, 0.26 mmol, 53%) as a white yellow solid. mp 113-117 °C (lit.,[154] 115 °C); δ_H (250 MHz; $CDCl_3$) 7.61-7.27 (5H, m, Ar-H), 7.58 (1H, d, J = 4.0, Thio-H), 7.24 (1H, d, J = 4.0, Thio-H), 2.5 (3H, s, CH_3); δ_C (62.9 MHz; $CDCl_3$) 190.6 (COMe), 152.78 (C), 143.1 (C), 133.5 (CH), 133.3 (C), 129.1 (CH), 129.1 (CH), 126.3 (CH), 123.9 (CH), 26.6 (CH_3); *m/z* (EI) 202.0 (52%, M^{+}), 187.0 (100%, M^{+}-Me).

Synthesis of 4-{1-[(2*R*,3*R*,4*S*,5*S*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl}benzoic acid, 133



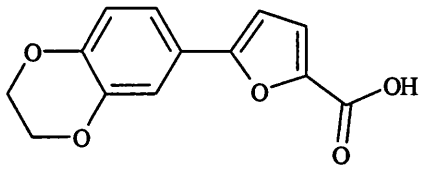
Following the general procedure A, to a solution of 5-iodouridine **131** (50.00 mg, 0.13 mmol) in deionised water (5 mL) were 4-carboxyphenylboronic acid (24.60 mg, 0.15 mmol), Na_2CO_3 (502μL, 0.75 mmol, 2M) and supported catalyst (46.98 mg, 3 mol%). The reaction was then heated at reflux for 4 h to yield compound **133** (11.31 mg, 0.03 mmol, 23%) after acidification with HCl, filtration and drying under high vacuum. ν_{max}(KBr disc)/cm^{-1} 3484 (N-H), 3047 (br, OH), 1695 (C=O), 1603 (C=O), 1517 (N-H), 782 (C=C); δ_H (300 MHz; d_6-DMSO) 13.00 (1H, br s, CO_2H), 11.64 (1H, s, NH), 8.95 (1H, s, C=CH), 7.78 (2H, d, *J* = 8.3, Ar-H), 7.77 (2H, d, *J* = 8.3, Ar-H), 5.90 (1H, d, *J* = 4.2, O-CH-N), 5.34 (3H, app s, OH), 4.10-4.22 (2H, m, C<u>H</u>-COH), 3.97 (1H, app d, *J* = 2.2, CH), 3.80-3.65 (2H, m, CH_2); δ_C (75.5 MHz; d_6-DMSO) 167.4 (CO_2H), 162.2 (C), 150.8 (C), 139.6 (CH), 138.0 (C), 130.8 (C), 129.5 (CH), 128.0 (CH), 112.6 (C), 89.0 (CH), 84.9 (CH), 74.5 (CH), 69.6 (CH), 60.4 (CH_2); *m/z* (FAB+) 365.1 (14%, MH^+).

Synthesis of 4-(2,3-dihydro-1,4-benzodioxin-6-yl)benzoic acid, 142



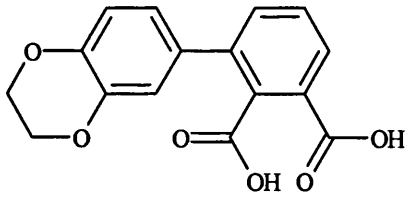
Following the general procedure A, to a solution of 4-iodophenyl carboxylic acid **109** (68.3 mg, 0.25 mmol) in deionised water (6 mL) were added 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid **116** (49.5 mg, 0.27 mmol), Na_2CO_3 (437 μL, 0.87 mmol, 2M) and the supported catalyst (87.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h to yield compound **142** (61.3 mg, 0.24 mmol, 96%) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp 215 – 217 °C; ν_{max}(KBr disc)/cm^{-1} 2878 (br, OH), 1675 (C=O), 1529 (C=C), 1497 (C=C); δ_H (300 MHz; d_6-DMSO) 13.95 (1H, br s, CO_2H), 7.95 (2H, d, J = 8.3, Ar-H), 7.70 (2H, d, J = 8.3, Ar-H), 7.21 (1H, app s, Ar-H), 7.18 (1H, d, J = 8.0, Ar-H), 6.94 (1H, d, J = 8.0, Ar-H), 4.26 (4H, app s, CH_2), ; δ_C (75.5 MHz; d_6-DMSO), 165.4 (CO_2H), 142.1 (CH), 142.0 (CH), 141.9 (CH), 130.4 (C), 128.1 (CH), 127.3 (C), 124.5 (CH), 118.1 (C), 115.9 (C), 113.6 (C), 62.4 (CH_2), 62.3 (CH_2); *m/z* (EI) 256.0 (6%, M^{+}) 247.8 (100%), Accurate Mass found: M^{+}, 256.0742 $C_{15}H_{12}O_4$ requires 256.0736.

Synthesis of 5-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-furoic acid, 144



Following the general procedure A, to a solution of 5-bromo-2-furoic acid **165** (23.8 mg, 0.12 mmol) in deionised water (5 mL) were added 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid **116** (24.7 mg, 0.14 mmol), Na_2CO_3 (219 μL, 0.42 mmol, 2M) and the supported catalyst (43.5 mg, 3 mol%). The reaction was then heated at reflux for 2 h to yield compound **144** (24.4 mg, 0.10 mmol, 85%) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp 206 – 207 °C; ν_{max}(KBr disc)/cm^{-1} 2873 (br, OH), 1694 (C=O), 1590 (C=C), 1534 (C=C); δ_H (250 MHz; d_6-DMSO) 13.00 (1H, br s, CO_2H), 7.29 - 7.31 (3H, m, Ar-H, Fur-H), 7.02 (1H, d, J = 3.6, Fur-H), 6.98 (1H, app d, J = 9.0, Ar-H), 4.23 (4H, app s, CH_2); δ_C (75.5 MHz; d_6-DMSO) 159.6 (CO_2H), 156.5, (C), 144.6 (C), 144.1 (C), 143.8 (C), 123.0 (C), 120.3 (CH), 119.9 (CH), 118.1 (CH), 113.4 (CH), 107.1 (CH), 64.6 (CH_2), 64.4 (CH_2); *m/z* (EI) 245.9 (100%, M^{+}), 200.9 (17%, M^{+}-CO_2H), Accurate Mass found: M^{+}, 246.0531 $C_{13}H_{10}O_5$ requires 246.0528.

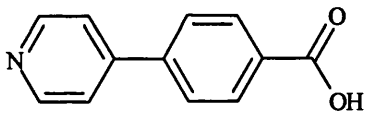
Synthesis of 3-(2,3-dihydro-1,4-benzodioxin-6-yl)phthalic acid, 143



Following the general procedure **A**, to a solution of 4-bromophthalic acid **164** (30.6 mg, 0.12 mmol) in deionised water (3 mL) were added 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid **116** (24.7 mg, 0.14 mmol), Na_2CO_3 (281 μL, 0.30 mmol, 2M) and the supported catalyst (43.5 mg, 3 mol%). The reaction was then heated at reflux for 2 h to

yield compound **143** (16.8 mg, 0.06 mmol, 47%) as a bright yellow solid after acidification with HCl, filtration and drying under vacuum. mp 186 – 187 °C; (Found: C, 61.70; H, 3.93 $C_{16}H_{12}O_6$+1/2(H_2O) requires C, 62.14; H, 4.24); ν_{max}(KBr disc)/cm^{-1} 2938 (br, OH), 1699 (C=O), 1673 (C=O), 1599 (C=C), 1673 (C=C); δ_H (300 MHz; d_6-DMSO) 13.15 (2H, br s, CO_2H), 7.70 – 7.79 (3H, m, Ar-H), 7.19 – 7.23 (2H, m, Ar-H), 6.95 (1H, d, J = 8.2, Ar-H), 4.27 (4H, app s, CH_2); δ_C (75.5 MHz; d_6-DMSO) 169.2 (CO_2H), 168.5 (CO_2H), 144.3 (C), 144.2 (C), 142.4 (C), 134.7 (C), 131.8 (C), 130.5 (C), 129.8 (CH), 128.3 (CH), 125.9 (CH), 120.2 (CH), 118.1 (CH), 115.8 (CH), 64.5 (CH_2), 64.4 (CH_2); *m/z* (FAB+) 300.0 (100%, M^+), Accurate Mass found: M^+, 300.0635 $C_{16}H_{12}O_6$ requires 300.0634.

Synthesis of 4-(4-pyridinyl)benzoic acid, 146[155]



- CsF as base

To a solution of 4-iodophenyl carboxylic acid **109** (62.0 mg, 0.25 mmol) in water (4 mL) were added Na_2CO_3 (125 µL, 0.25 mmol, 2M) and CH_3CN (1.75 mL). Then 4-pyridinyl boronic acid **114** (33.8 mg, 0.27 mmol), the supported catalyst (87.0 mg, 3 mol%) and CsF (95.0 mg, 0.62 mmol) were added to the reaction mixture. The solution was heated at reflux for 2.5 h. The supported catalyst was then separated from the reaction mixture by decantation. CH_3CN was removed under reduced pressure and the remaining aqueous solution was extracted with Et_2O (2 × 5 mL) and acidified with HCl (1 - 2 mL, 2N), compound **146** started to appear as fine brown needles after 15 min, which were isolated

after filtration. The filtrate gave again after 5 min more fine brown needles, which was isolated after filtration. The solids were united and were dried under high vacuum to yield compound **146** (32.3 mg, 0.16 mmol, 65%). mp > 305 °C (lit.,[155] 210 °C); ν_{max}(KBr disc)/cm^{-1} 3096 (br, OH), 1707 (C=O); δ_H (300 MHz; d_6-DMSO) 13.35 (1H, br s, CO_2H), 8.94 (2H, *J* = 6.7, d, Pyr-H), 8.32 (2H, *J* = 6.7, d, Pyr-H), 8.10 (4H, app s, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 167.8 (CO_2H), 153.8 (C), 145.3 (CH), 140.0 (C), 133.9 (CH), 131.4 (CH), 129.2 (CH), 124.9 (C); *m/z* (EI) 199.1 (100%, M^{+}), 154.1 (34%, M^{+}-CO_2H), Accurate Mass found: M^{+}, 199.0639 $C_{12}H_9NO_2$ requires 199.0633.

- K_3PO_4 as base

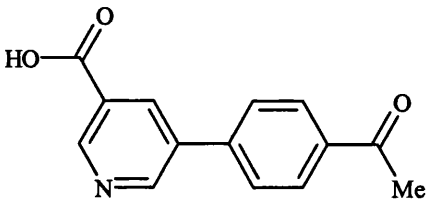
To a mixture of 4-iodophenyl carboxylic acid **109** (62.0 mg, 0.25 mmol) in water (4 mL) were added Na_2CO_3 (125 μL, 0.25 mmol, 2M) and CH_3CN (1.75 mL). Then 4-pyridinyl boronic acid **114** (33.8 mg, 0.27 mmol), the supported catalyst (87.0 mg, 3 mol%) and K_3PO_4 (312 μL, 0.62 mmol, 2M) were added to the mixture. The solution was heated at reflux for 2.5 h. The supported catalyst, which was stuck to the pressure tube, was then separated from the mixture by simply pouring the aqueous solution. CH_3CN was removed under reduced pressure and the remaining aqueous solution extracted with Et_2O (2 × 5 mL), acidified with HCl (1 - 2 mL, 2N), and compound **146** (3.00 mg, 0.015 mmol, 6%) was isolated after filtration and drying under high vacuum as brown solid. Data were identical to that reported previously.

- NaOH as base

Following the same procedure as just described previously, to a mixture of 4-iodophenyl carboxylic acid **109** (62.0 mg, 0.25 mmol) in water (4 mL) was added Na_2CO_3 (125 μL,

0.25 mmol, 2M) and CH_3CN (1.75 mL). Then 4-pyridinyl boronic acid **114** (33.8 mg, 0.27 mmol), the supported catalyst (87.0 mg, 3 mol%) and NaOH (312 μL, 0.62 mmol, 2M) were added to the mixture. The solution was heated at reflux for 2.5 h and the supported catalyst was then separated from the mixture by decantation. CH_3CN was removed under reduced pressure and the remaining aqueous solution was extracted with Et_2O (2 × 5 mL), acidified with HCl (1 - 2 mL, 2N) and compound **146** (13.9 mg, 0.07 mmol, 28%) was isolated after filtration and drying under high vacuum. Data were identical to that reported previously.

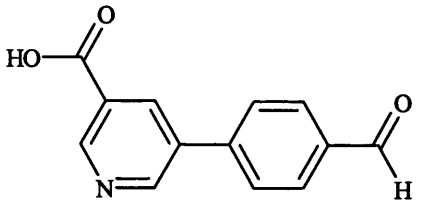
Synthesis of 5-(4-acetylphenyl)nicotinic acid, 147



Following the general procedure A, to a solution of 5-bromonicotinic acid **167** (101.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-acetylphenylboronic acid **113** (90.2 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M) and the supported catalyst (58.0 mg, 1 mol%). The reaction was then heated at reflux for 2 h to yield compound **147** (101.0 mg, 0.47 mmol, 84 %) as a white cream solid after acidification with HCl, filtration and drying under vacuum. mp 261-262 °C; ν_{max}(KBr disc)/cm^{-1} 3052 (OH), 1695 (C=O), 1684 (C=O), 1607 (C=C), 1511.3 (C=C); δ_H (250 MHz; d_6-DMSO) 13.7 (1H, br s, CO_2H), 9.36 (1H, app d, J = 2.3, Pyr-H), 9.17 (1H, app d, J = 1.9, Pyr-H), 8.59 (1H, app t, J = 2.3, Pyr-H), 8.16 (2H, d, J = 8.4, Ar-H), 8.03 (2H, d, J = 8.4, Ar-H), 2.70 (3H, *s*, CH_3); δ_C (62.90 MHz; d_6-DMSO) 197.8 (COMe), 166.1 (CO_2H), 151.5 (CH), 149.6

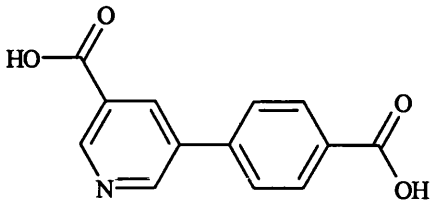
(CH), 140.4 (C), 136.45 (C), 134.8 (C), 134.4 (CH), 129.0 (CH), 127.4 (CH), 126.8 (C), 26.8 (CH_3); *m/z* (EI) 241.0 (22%, M^+), 226.0 (79%, M^+-Me), 121.0 (100%), Accurate Mass found: M^+, 241.0741 $C_{14}H_{11}NO_3$ requires 241.0739.

Synthesis of 5-(4-formylphenyl)nicotinic acid, 154



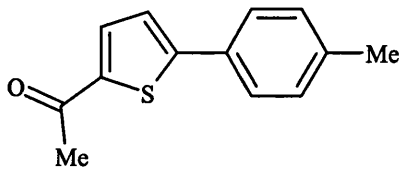
Following the general procedure A, to a solution of 5-bromonicotinic acid **167** (101.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-formylphenylboronic acid **119** (82.5 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M) and the supported catalyst (58.0 mg, 1 mol%). The reaction was then heated at reflux for 2.5 h to yield compound **154** (77.0 mg, 0.34 mmol, 68 %) as a bright yellow solid after acidification with HCl, filtration and drying under vacuum. mp 229 – 230 °C; ν_{max}(KBr disc)/cm^{-1} 3055 (br, OH), 2852 (OC-H), 1696 (C=O), 1685 (C=O), 1607 (C=C), 1512 (C=C); δ_H (300 MHz; d_6-DMSO) 13.40 (1H, s, CO_2H), 10.10 (1H, s, CHO), 9.22 (1H, app d, J = 2.0, Pyr-H), 9.12 (1H, app d, J = 1.4, Pyr-H), 8.56 (1H, app s, Pyr-H), 8.07 (4H, app s, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 192.8 (CHO), 166.0 (CO_2H), 151.5 (CH), 149.8 (CH), 141.7 (C), 135.8 (C), 135.0 (CH), 134.3 (C), 130.2 (CH), 127.9 (CH), 126.8 (C); *m/z* (FAB+) 228.1 (100%, M+H), Accurate Mass found: M+H, 228.0657 $C_{13}H_9NO_3$ requires 228.0661.

Synthesis of 5-(4-carboxyphenyl)nicotinic acid, 128



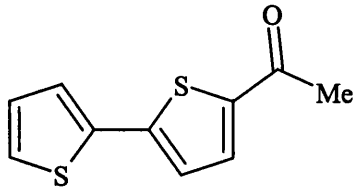
Following the general procedure A, to a solution of 5-bromonicotinic acid **167** (101.0 mg, 0.50 mmol) in deionised water (10 mL) were 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1,125 mL, 2.25 mmol, 2M) and the supported catalyst (58.0 mg, 1 mol%). The reaction was then heated at reflux for 2 h to yield compound **128** (102.0 mg, 0.42 mmol, 84 %) as a solid after acidification with HCl, filtration and drying under vacuum. The purification was carried out by following procedures B and C, which gave compound **128** as a colourless solid (32.4 mg, 0.14 mmol, 28%). mp >307 °C; (Found: C, 60.90; H, 3.60; N, 5.33 $C_{13}H_9NO_4$+3/4(H_2O) requires C, 60.82; H, 4.12; N, 5.46); ν_{max}(KBr disc)/cm^{-1} 3086 (br, OH), 1694 (C=O), 1681 (C=O), 1609 (C=C), 1513 (C=C); δ_H (250 MHz; d_6-DMSO) 13.40 (2H, br s, CO_2H), 9.18 (1H, app d, J = 2.2, Pyr-H), 9.11 (1H, app d, J = 1.8, Pyr-H), 8.53 (1H, app t, J = 2.0, Pyr-H), 8.08 (2H, d, J = 8.3, Ar-H), 7.95 (2H, d, J = 8.3, Ar-H); δ_C (75.5 MHz; d_6-DMSO) 167.3 (CO_2H), 166.3 (CO_2H), 151.5 (CH), 149.7 (CH), 140.4 (C), 135.4 (CH), 134.9 (C), 131.0 (C), 130.5 (CH), 127.7 (CH), 127.3 (C); *m/z* (EI) 243.1 (100%, M^{+}), Accurate Mass found: M^{+}, 243.0538 $C_{13}H_9NO_4$ requires 243.0532.

Synthesis of 1-[5-(4-methylphenyl)-2-thienyl]-1-ethanone, 150[156]



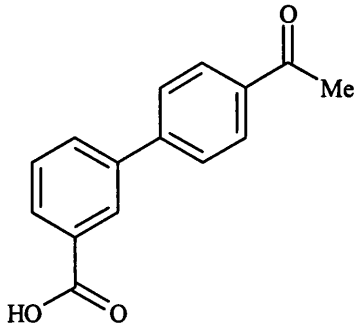
Following the general procedure A, to a solution 2-acetyl-5-bromothiophene **174** (76.8 mg, 0.37 mmol) in deionised water (9 mL) were added 4-methylbenzeneboronic acid **117** (56.1 mg, 0.41 mmol), Na_2CO_3 (469 μL, 0.92 mmol, 2M,) and the supported catalyst (43.5 mg, 1 mol%). The reaction was then heated at reflux for 3 h. The hot reaction mixture was then filtrated to separate the catalyst from the solution. When cooling a solid precipitated, which was then isolated by filtration. The solid was purified by column chromatography (SiO_2, Petrol then petrol/ethyl acetate 90/10) to yield compound **150** (66.6 mg, 0.30 mmol, 82 %) as a colourless solid. mp 115 – 117 °C (lit.,[156] 116 – 118 °C); δ_H (300 MHz; $CDCl_3$) 7.56 (1H, d, J = 4.0, Thio-H), 7.46 (2H, d, J = 8.0, Ar-H), 7.19 (1H, d, J = 4.0, Thio-H), 7.14 (2H, d, J = 8.0, Ar-H), 2.47 (3H, s, Thio-$COCH_3$), 2.30 (3H, s, Ar-CH_3); δ_C (75.5 MHz; $CDCl_3$) 190.98 (COMe), 153.5 (C), 142.9 (C), 139.6 (C), 133.9 (CH), 130.9 (C), 130.2 (CH), 126.5 (CH), 123.8 (CH), 26.9 (CH_3), 21.7 (CH_3); *m/z* (EI) 216.1 (58%, M^+), 201.0 (100%, M^+-Me).

Synthesis of 1-[5-(2-thienyl)-2-thienyl]-1-ethanone, 152[157]



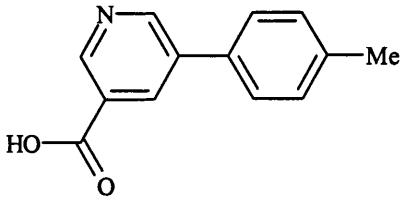
Following the general procedure A, to a solution 2-acetyl-5-bromothiophene **174** (64.6 mg, 0.31 mmol) in deionised water (9 mL) were added 2-thienylboronic acid **118** (44.4 mg, 0.37 mmol), Na_2CO_3 (387 μL, 0.77 mmol, 2M) and the supported catalyst (35.7 mg, 1 mol%). The reaction was then heated at reflux for 3 h. The hot reaction mixture was then filtrated to separate the catalyst from the solution. When cooling a solid precipitated, which was then isolated by filtration. The solid was purified by column chromatography (SiO_2, petrol then petrol/ethyl acetate 90/10) to yield compound **152** (22.3 mg, 0.10 mmol, 34 %) as a white beige solid. mp 118 – 120 °C (lit.,[157] 108 – 111 °C); δ_H (300 MHz; $CDCl_3$) 7.55 (1H, d, J = 3.9, COMeThio-H), 7.47 (1H, dd, J = 1.3, 2.9, Thio-H), 7.32 (1H, dd, J = 2.9, 5.0, Thio-H), 7.27 (1H, dd, J = 1.3, 5.0, Thio-H), 7.13 (1H, d, J = 3.9, COMeThio-H), 2.49 (3H, s, $COCH_3$); δ_C (75.5 MHz; $CDCl_3$) 190.9 (COMe), 147.7 (C), 142.6 (C), 135.1 (C), 133.8 (CH), 127.4 (CH), 126.3 (CH), 124.3 (CH), 122.4 (CH), 68.5 (CH_3); *m/z* (EI) 208.0 (71%, M^+), 193.0 (100%, M^+-Me).

Synthesis of 4'-acetyl[1,1'-biphenyl]-3-carboxylic acid, 148



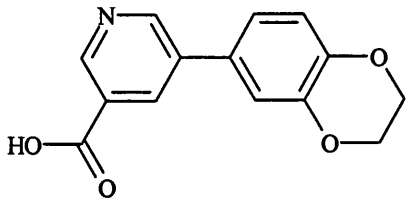
Following the general procedure A, to a solution of 3-iodophenyl carboxylic acid **172** (124.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-acetylphenylboronic acid **113** (90.2 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M) and the supported catalyst (58.0 mg, 1 mol%). The reaction was then heated at reflux for 3 h to yield compound **148** (96.6 mg, 0.40 mmol, 80 %) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp 190 – 193 °C; ν_{max}(KBr disc)/cm^{-1} 2966 (br, OH), 1699 (C=O), 1683 (C=O), 1605 (C=C), 1512 (C=C); δ_H (300 MHz; d_6-DMSO) 13.20 (1H, br s, CO_2H), 8.23 (1H, app t, J = 1.6, Ar-H), 8.05 (2H, d, J = 8.5, Ar-H), 7.98 (2H, app dd, J = 1.6, 7.8, Ar-H), 7.85 (2H, d, J = 8.5, Ar-H), 7.63 (1H, app t, J = 7.8, Ar-H), 2.60 (3H, s, $COCH_3$); δ_C (75.5 MHz; d_6-DMSO) 197.8 (COMe), 167.4 (CO_2H), 143.9 (C), 139.6 (C), 136.3 (C), 132.1 (C), 131.7 (CH), 129.8 (CH), 129.4 (CH), 129.3 (CH), 127.9 (CH), 127.4 (CH), 27.1 (CH_3); *m/z* (EI) 240.1 (43%, M^{+}), 225.0 (100%, M^{+}-Me), Accurate Mass found: M^{+}, 240.0782 $C_{15}H_{12}O_3$ requires 240.0786.

Synthesis of 5-(4-methylphenyl)nicotinic acid, 151



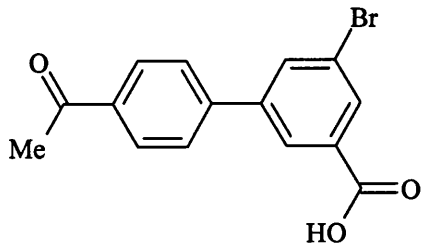
Following the general procedure A, to a solution of 5-bromonicotinic acid **167** (101.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-methylbenzeneboronic acid **117** (75.0 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M) and the supported catalyst (58.0 mg, 1 mol%). The reaction was then heated at reflux for 2 h to yield compound **151** (32.0 mg, 0.15 mmol, 30 %) as a colourless solid after acidification with HCl, filtration and drying under vacuum. mp 264 – 266 °C; (Found: C, 70.20; H, 5.02; N, 6.34 $C_{13}H_{11}NO_2$+1/2(H_2O) requires C, 70.26; H, 5.44; N, 6.30); ν_{max}(KBr disc)/cm^{-1} 3075 (br, OH), 1693 (C=O), 1582 (C=C), 1516 (C=C); δ_H (400 MHz; d_6-DMSO) 13.53 (1H, br *s*, CO_2H), 9.07 (1H, d, *J* = 2.3, Pyr-H), 9.02 (1H, d, *J* = 2.0, Pyr-H), 8.41 (1H, app t, *J* = 2.1, Pyr-H), 7.68 (2H, d, *J* = 8.0, Ar-H), 7.33 (2H, d, *J* = 8.0, Ar-H), 2.37 (3H, s, CH_3); δ_C (75.5 MHz; d_6-DMSO) 167.1 (CO_2H), 151.9 (CH), 149.5 (CH), 139.0 (C), 136.3 (C), 135.0 (CH), 134.0 (C), 130.7 (CH), 127.7 (CH), 127.5 (C), 21.6 (CH_3); *m/z* (EI) 213.0 (100%, M^+), 168.0 (14%, M^+-Me), Accurate Mass found: M^+, 213.0786 $C_{13}H_{11}NO_2$ requires 213.0790.

Synthesis of 5-(2,3-dihydro-1,4-benzodioxin-6-yl)nicotinic acid, 145



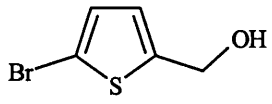
Following the general procedure A, to a solution of 5-bromonicotinic acid **167** (101.0 mg, 0.50 mmol) in deionised water (10 mL) were added 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid **116** (99.0 mg, 0.55 mmol), Na_2CO_3 (875 μL, 1.75 mmol, 2M) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 2 h to yield compound **145** (32.9 mg, 0.13 mmol, 26 %) as a cream brown solid after acidification with HCl, filtration and drying under vacuum. mp 279 – 282 °C; ν_{max}(KBr disc)/cm^{-1} 2941 (br, OH), 1698 (C=O), 1517 (C=C); δ_H (300 MHz; d_6-DMSO) 13.44 (1H, br s, CO_2H), 9.01 (1H, app s, Pyr-H), 8.95 (1H, app s, Pyr-H), 8.33 (1H, app s, Pyr-H), 7.27 (1H, app s, Ar-H), 7.22 (1H, d, J = 8.3, Ar-H), 6.96 (1H, d, J = 8.3, Ar-H), 4.26 (4H, app s, CH_2); δ_C (75.5 MHz; d_6-DMSO) 167.1 (CO_2H), 151.8 (CH), 149.2 (CH), 144.9 (C), 144.8 (C), 135.8 (C), 134.8 (CH), 130.0 (C), 127.5 (C), 120.9 (CH), 118. 8 (CH), 116.4 (CH), 65.1 (CH_2), 64.9 (CH_2); *m/z* (EI) 257.0 (100%, M^+), Accurate Mass found: M^+, 257.0701 $C_{14}H_{11}NO_4$ requires 257.0688.

Synthesis of 4'-acetyl-5-bromo[1,1'-biphenyl]-3-carboxylic acid, 149



Following the general procedure A, to a solution of 3-bromo-5-iodobenzoic acid **175** (163.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-acetylphenylboronic acid **113** (90.2 mg, 0.55 mmol), Na_2CO_3 (2M, 0.17 mmol, 900 μL) and the supported catalyst (174.0 mg, 3 mol%). The reaction was then heated at reflux for 3 h to yield compound **149** (121.7 mg, 0.31 mmol, 62%) as a crude solid after acidification with HCl, filtration and drying under vacuum. The purification was carried out by following procedures B and C, which gave compound **149** as a colourless solid (16.4 mg, 0.05 mmol, 10%). mp 193 – 195 C; ν_{max}(KBr disc)/cm^{-1} 3070 (br, OH), 1716 (MeC=O), 1682 (C=O), 1449 (C=C); δ_H (300 MHz; DMSO) 13.40 (1H, br s, CO_2H), 8.19 (2H, app s, Ar-H), 8.04 (3H, app d, *J* = 7.3, Ar-H), 7.88 (2H, app d, J = 7.5, Ar-H), 2.60 (3H, s, CH_3); δ_C (75.5 MHz; DMSO) 198.4 (COMe), 166.6 (CO_2H), 142.8 (C), 142.4 (C), 137.2 (C), 134.6 (C), 134.5 (CH), 132.2 (CH), 129.8 (CH), 128.2 (CH), 127.5 (CH), 123.5 (C), 27.7 (CH_3); *m/z* (EI) 317.8/319.8 (M^+, 39/39%), 302.8/304.8 (100%), Accurate Mass found: M^+, 317.9882 $C_{15}H_{11}O_3Br$ requires 317.9891.

Synthesis of 2-bromo-5-hydroxymethylthiophene, 156[158]



- Reduction with B_2H_6

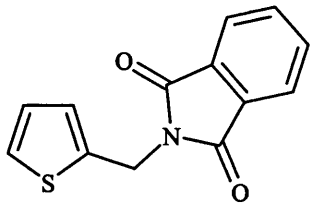
To a solution of 5-bromo-2-thiophene carboxylic acid **165** (1.00 g, 4.80 mmol) in THF (2 mL) at 0 °C under nitrogen, was added dropwise over 15 min. a solution of B_2H_6 in THF (6.5 mL, 6.5 mmol, 1M). After addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a mixture of water: THF (1:1, 5 mL) and a saturated solution of K_2CO_3 (5 mL) was added. The mixture was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, DCM) to yield compound **156** (193.0 mg, 1.00 mmol, 21%) as a colourless oil. δ_H (250 MHz; $CDCl_3$) 6.92 (1H, d, *J* = 3.7, Thio-H), 6.75 (1H, d, *J* = 3.7, Thio-H), 4.70 (2H, d, *J* = 0.7, CH_2), 2.75 (1H,br s, OH); *m/z* (EI) 191.9/193.9 (M^+, 55/55%), 113.0 (100%, M^+-Br).

- Reduction with $NaBH_4$

To a solution of 5-bromo-2-thiophenecarboxaldehyde **157** (2.00 g, 10.5 mmol) in MeOH (10 mL) at 0 °C was added a solution of $NaBH_4$ in MeOH (6 ml, 15.8 mmol, 2.6 M). After addition, the reaction was allowed to stir for 5 h at room temperature. The solvent was then removed under reduced pressure. The residue was quenched with water (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was then

purified by distillation under reduced pressure to yield compound **156** (1.01 g, 5.25 mmol, 50%) as a colourless oil. bp 39 – 44 °C at 5 mmHg. Data were identical to that reported previously.

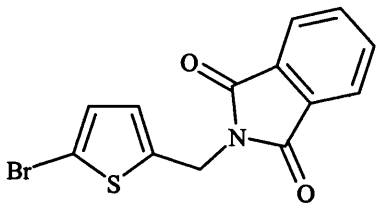
Synthesis of 2-(2-thienylmethyl)-1*H*-isoindole-1,3(2*H*)-dione, 162[138]



To a solution of 2-hydroxymethylthiophene **161** (1.00 g, 8.85 mmol) in anhydrous THF (20 mL) were added under nitrogen phthalimide **159** (1.40 g, 9.73 mmol) and triphenylphosphine (2.50 g, 9.73 mmol). Di-isopropyl azidodicarboxylate (1.90 g, 9.73 mmol) was then slowly added to the reaction mixture. The mixture was stirred at room temperature for 72 h and the reaction was quenched by the addition of brine (30 mL). The aqueous layer was washed with Et_2O (2 × 50 mL), the combined organic fractions were dried over Na_2SO_4 anhydrous and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petrol then petrol/ethyl acetate 90/10), followed by recrystallisation from ethanol to yield compound **162** (684.3 mg, 2.81 mmol, 35%) as a colourless solid. mp 125 - 126 °C (from ethanol) (lit.,[138] 124 – 125 °C); δ_H (300 MHz; $CDCl_3$) 7.78-7.61 (4H, m, Ar-H), 7.13 (1H, dd, J = 1.2, 5.1, Thio-H), 7.07 (1H, app d, J = 3.5, Thio-H), 6.85 (1H, dd, J = 3.5, 5.1, Thio-H), 4.95 (2H, s, CH_2); δ_C (75.5 MHz; $CDCl_3$) 168.0 (CO), 138.4 (C), 134.5 (CH), 132.4 (C), 128.1 (CH), 127.3

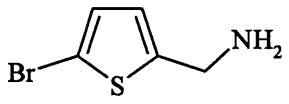
(CH), 126.3 (CH), 123.8 (CH), 36.1 (CH_2); *m/z* (EI) 243.0 (100%, M^+), Accurate Mass found: M^+, 243.0352 $C_{13}H_9NO_2S$ requires 243.0354.

Synthesis of 2-[(5-bromo-2-thienyl)methyl]-1*H*-isoindole-1,3(2*H*)-dione, 160[138]



To a solution of compound **162** (282.2 mg, 1.16 mmol) in acetic acid (23 mL) was added bromine (204.0 mg, 1.28 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue was then dissolved in DCM, washed successively with a solution of sodium hydrogencarbonate, and water. The organic phase was dried over Na_2SO_4 anhydrous and the solvent was then reduced under pressure. The residue was recrystallised from ethanol to yield compound **160** (361.3 mg, 1.12 mmol, 97%) as a colourless crystalline solid. mp 109 – 111 °C (from ethanol) (lit.,[138] 100 °C); δ_H (300 MHz; $CDCl_3$) 7.60 - 7.80 (4H, m, Ar-H), 6.82 (1H, d, *J* = 3.7, Thio-H), 6.78 (1H, d, *J* = 3.7, Thio-H), 4.83 (2H, s, CH_2); δ_C (75.5 MHz; $CDCl_3$) 167.8 (CO), 140.0 (C), 134.6 (CH), 132.3 (C), 130.0 (CH), 128.6 (CH), 123.9 (CH), 113.0 (C), 36.2 (CH_2); *m/z* (EI) 322.9/324.9 (25/25%, M^+), 242.0 (100%, M^+-Br).

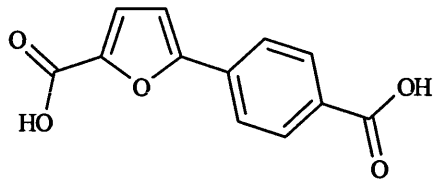
Synthesis of (5-bromo-2-thienyl)methylamine, 155



To a solution of compound **160** (88.7 mg, 0.27 mmol) in ethanol (5 mL) was added hydrazine hydrate (14.0 mg, 0.27 mmol) and the reaction mixture heated at reflux. After 1.5 h, an excess of HCl (0.5 mL, concentrated 37%) was added to the mixture and the heating carried on for a further 30 min. The solvent was then removed under reduced pressure, the residue was dissolved in a solution of NaOH (5 mL, concentrated), saturated with Na_2CO_3 and continuously extracted with Et_2O. Finally, the solvent was removed under reduced pressure to yield a solid, which was recrystallised from ethanol to give compound **155** as a white cream crystalline solid (26.3 mg, 1.37 mmol, 50%). mp 184 – 188 °C (from ethanol); ν_{max}(KBr disc)/cm^{-1} 3426 (br, N-H), 796 (C-Br); δ_H (300 MHz; $CDCl_3$) 6.81 (1H, d, J = 3.7, Thio-H), 6.60 (1H, d, J = 3.7, Thio-H), 3.92 (2H, s, CH_2), 1.69 (2H, br s, NH_2); δ_C (75.5 MHz; $CDCl_3$) 148.1 (C), 129.6 (CH), 122.8 (CH), 109.4 (C), 40.7 (CH_2); *m/z* (FAB+) 191.1/193.1 (M+H, 28/30%), 175.1/177.1 (M+H-NH_2, 23/27%), 73.0 (100%), Accurate Mass found: M+H, 191.0780 C_5H_6NSBr requires 191.0783.

4.2.2 Procedure for the recycling tests

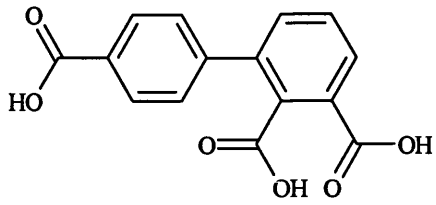
For the synthesis of 5-(4-carboxyphenyl)-2-furoic acid, 127



To a solution of 5-bromo-2-furoic acid **165** (47.7 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.6 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the supported catalyst (87.0 mg, 3 mol%). The reaction was heated at reflux for 1 h. The supported catalyst was separated from the solution by decantation, the aqueous phase was extracted with Et_2O and acidified with HCl as previously reported in procedure A, to yield compound **127** (53.0 mg, 0.45 mmol, 91%) after filtration and drying under high vacuum.

Following the same procedure, the supported catalyst was directly reintroduced into a solution containing the same amount of reagents, and the reaction was heated at reflux for 17 h to give **127** (14.4 mg, 0.33 mmol, 66%). Data were identical to that reported previously. The procedure for the third use of the supported catalyst was identical to the second use. The reaction was put at reflux for 23 h and no product was isolated.

For the synthesis of [1,1'-biphenyl]-2,3,4'-tricarboxylic acid, 126



To a solution 4-bromophthalic acid **164** (122.5 mg, 0.50 mmol) in deionised water (10 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1375 μL, 2.75 mmol, 2M,) and the supported catalyst (174.0 mg, 3 mol%). The reaction was heated at reflux for 1.5 h. The supported catalyst was separated from the solution by decantation, the aqueous phase was extracted with Et_2O and acidified with HCl as previously reported in procedure A, to yield compound **126** (138.7 mg, 0.48 mmol, 97%) after filtration and drying under high vacuum.

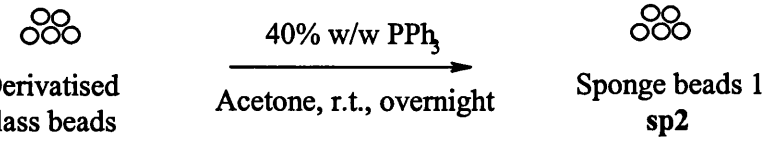
Following the same procedure, the supported catalyst was directly reintroduced into a solution containing the same amount of reagents, and the reaction was heated at reflux for 1.5 h to give **126** (134.4 mg, 0.47 mmol, 94%). The procedure for the third use of the supported catalyst was identical to the second use. The reaction was heated at reflux for 20 h and no product was isolated. Data were identical to that reported previously.

4.2.3 Typical Procedure for the preparation and testing of the sponge beads

Without triphenylphosphine: sp1

sp1 was prepared following the same procedure as for the derivatised glass beads.

With triphenylphosphine: sp2



Derivatised glass beads → Sponge beads 1 **sp2**

To a mixture of the derivatised glass beads (2.50 g) in acetone (12.5 mL), was added triphenylphosphine (1.00 g, 3.81 mmol). The reaction mixture was then stirred at room temperature overnight and the solvent was removed under reduced pressure to yield a fine white powder (2.43 g), which was dried under high vacuum.

Typical procedure for initial test for the removal of $Pd(PPh_3)_4$ with the sponge bead

To a round bottom flask were introduced water (5 mL) and $Pd(PPh_3)_4$ (19.0 mg, 0.02 mmol). The mixture was then stirred for 5 min. under nitrogen. The derivatised glass beads (190.0 mg) were added to the mixture and stirred for 10 min. After filtration, the solution was analysed for palladium content.

Procedure for initial test for the removal of $Pd(PPh_3)_4$ by extraction with Et_2O

To a round bottom flask were introduced water (5 mL) and $Pd(PPh_3)_4$ (19.0 mg, 0.02 mmol). The mixture was then stirred for 5 min under nitrogen. The aqueous solution was then extracted with Et_2O (2 × 5 mL) and, the aqueous solution was analysed for palladium content after filtration.

Typical procedure for the use of sponge beads in work up

Following the general procedure A, to a solution of the organohalide (0.50 mmol) in water (5 mL) were added the boronic acid (0.55 mmol), Na_2CO_3 (1,125 mL, 2.25 mmol,

2M,) and $Pd(PPh_3)_4$ (17.4 mg, 1.50 μmol, 3 mol%). The reaction was heated at reflux until completion of the reaction. To the cooled solution was then added the sponge beads **sp1** ***or*** **sp2** (174.0 mg), and the mixture was stirred for 10 min. The sponge beads were separated from the solution by filtration, the aqueous phase was acidified and the product was analysed for palladium content after filtration and drying under high vacuum.

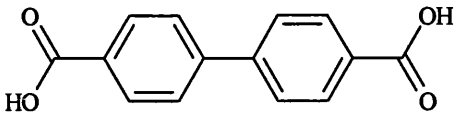
4.2.4 Procedure for the preparation of the normal phase glass beads catalyst

PdX_2
on normal phase bead
X= Cl-, OAc-

To a solution of palladium chloride (27.0 mg, 0.15 mmol) or palladium acetate (32.8 mg, 0.15 mmol) in methanol (10 mL) was added trisulfonated triphenylphosphine (170.6 mg, 0.30 mmol). The reaction mixture was stirred at 55 °C under nitrogen for 2 h. Davisil 500 Å (2.00 g) was then added to the reaction mixture and stirred at room temperature for a further 1 h. The solvent was then removed under reduced pressure to yield a fine powder. The $PdCl_2$ beads produced a beige powder, while the $Pd(OAc)_2$ beads yielded a grey beige powder.

4.2.5 Procedure for biphasic reaction promoted by ultrasound or heat

Synthesis of [1,1'-biphenyl]-4,4'-dicarboxylic acid, 120



Typical procedure D by ultrasound

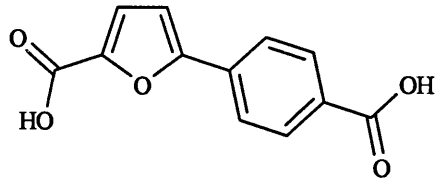
To a solution of 4-iodophenyl carboxylic acid **109** (124.0 mg, 0.50 mmol) in deionised water (10 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. $Pd(PPh_3)_4$ (17.4 mg, 0.015 mmol) and toluene (5 mL) were then added to the solution and a constant flow of nitrogen was maintained during the reaction. The ultrasound horn was placed at the interface of both phases and the ultrasound switched on for a period of 2 h, with a 50% duty cycle. The emulsion was allowed to cool down and to give back the two phases. The aqueous phase was then separated from the organic phase, extracted with Et_2O (2 × 5 mL) and acidified with HCl (concentrated 37%), to give compound **120** (100% of conversion) after filtration. Data were identical to that reported previously.

Typical procedure E by heating

To a solution of 4-iodophenyl carboxylic acid **109** (124.0 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) and toluene (5 mL) were then added to the solution. The reaction was heated at reflux for 2 h and with a vigorous stirring. The aqueous phase was separated from the organic phase, extracted with Et_2O (2 × 5 mL) and acidified with

HCl (concentrated 37%), to give compound **120** (100% conversion) after filtration. Data were identical to that reported previously.

Synthesis of 5-(4-carboxyphenyl)-2-furoic acid, 127



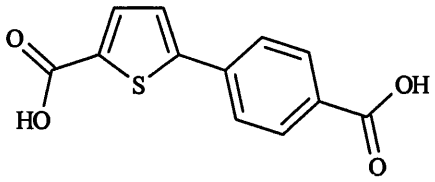
By ultrasound

Following procedure D, to a solution 5-bromo-2-furoic acid **165** (47.7 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.6 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. Then $Pd(PPh_3)_4$ (8.6 mg, 0.015 mmol) and toluene (5 mL) were added to the solution. The ultrasound horn was placed at the interface of both phases and the ultrasound switched on for a period of 2 h, with a 50% duty cycle. Compound **127** (88% of conversion) was then isolated after acidification with HCl and filtration. Data were identical to that reported previously.

By heating

Following procedure E, to a solution of 5-bromo-2-furoic acid **165** (47.7 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (45.5 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. Then $Pd(PPh_3)_4$ (8.6 mg, 0.015 mmol) and toluene (5 mL) were added to the solution. The reaction was heated at reflux for 2 h, but no product was isolated.

Synthesis of 5-(4-carboxyphenyl)-2-thiophenecarboxylic acid, 129



By ultrasound

Following procedure D, to a solution 5-bromo-2- thiophene carboxylic acid **158** (102.5 mg, 0.50 mmol) in deionised water (5 mL) were added 4-carboxyphenylboronic acid **115** (91.3 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. Then $Pd(PPh_3)_4$ (8.7 mg, 0.015 mmol) and toluene (5 mL) were added to the solution. The ultrasound horn was placed at the interface of both phases and the ultrasound switched on for a period of 2 h, with a 50% duty cycle. Compound **129** (79% of conversion) was then isolated after acidification with HCl and filtration. Data were identical to that reported previously.

By heating

Following procedure E, to a solution of water (5 mL), 5-bromo-2-thiophene carboxylic acid **158** (102.5 mg, 0.50 mmol), 4-carboxyphenylboronic acid **115** (91.2 mg, 0.55 mmol), Na_2CO_3 (1.125 mL, 2.25 mmol, 2M,) and the solution was purged with nitrogen. Then $Pd(PPh_3)_4$ (8.6 mg, 0.015 mmol) and toluene (5 mL) were added to the solution. The reaction was put at reflux for 2 h, and gave product **129** (89% conversion). Data were identical to that reported previously.

4.2.6 Typical procedure for the scale up

Derivatisation of the Glass beads

Derivatised
glass beads

To a mixture of Davisil 500Å (50.00 g) and absolute acetone (250 mL) was added octyl trimethoxysilane 112 (41.5 mL). The mixture was stirred overnight at room temperature and under nitrogen. The derivatised silica (49.80 g) was then collected as a fine white powder after removal of the solvent under reduced pressure and drying under high vacuum.

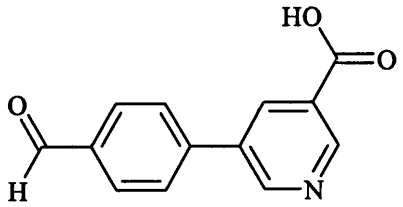
Loading of $Pd(PPh_3)_4$ onto the derivatised glass beads

$Pd(PPh_3)_4$
on beads

To a mixture of the derivatised glass beads (50.00 g) in cyclohexane (500 mL) under nitrogen was added a mixture of $Pd(PPh_3)_4$ (5.00 g, 4.00 mmol) in cyclohexane (500 mL), the mixture was then transferred under nitrogen, through a canula to the mixture containing the derivatised glass beads. The whole mixture was then stirred at room temperature overnight under nitrogen. The solvent was then removed under reduced

pressure to yield a fine grey brown powder (49.75 g), which was dried under high vacuum.

Synthesis of 5-(4-formylphenyl) nicotinic acid, 154



To a solution of 5-bromonicotinic acid **167** (10.10 g, 50.00 mmol) in of deionised water (1 L), was added Na_2CO_3 (25.0 mL 50.00 mmol, 2M) and the reaction mixture stirred until most of the 5-bromonicotinic acid **167** was solubilised. The supported catalyst (8.70 g, 1.5 mol%), 4-formylphenylboronic acid **119** (8.25 g, 55.00 mmol) and Na_2CO_3 (67.5 mL, 125.00 mmol, 2M) were then added to the mixture. The reaction was then refluxed for 48 hours. Once the reaction was cooled to room temperature and the catalyst settled down in the flask (and / or floating at the surface of the solution), the solution was separated from the catalyst by pouring carefully the solution. The aqueous phase was extracted with Et_2O (2 × 200-300 mL). The aqueous layer was acidified with HCl (37%) until complete precipitation of the product (during this step, there is a strong evolution of CO_2 due to the base and the product starts precipitating when the evolution of gas is almost complete). The solid was then collected by filtration and dried under high vacuum to yield compound **154** (8.90 g, 39.00 mmol, 78%). Data were identical to that reported previously.

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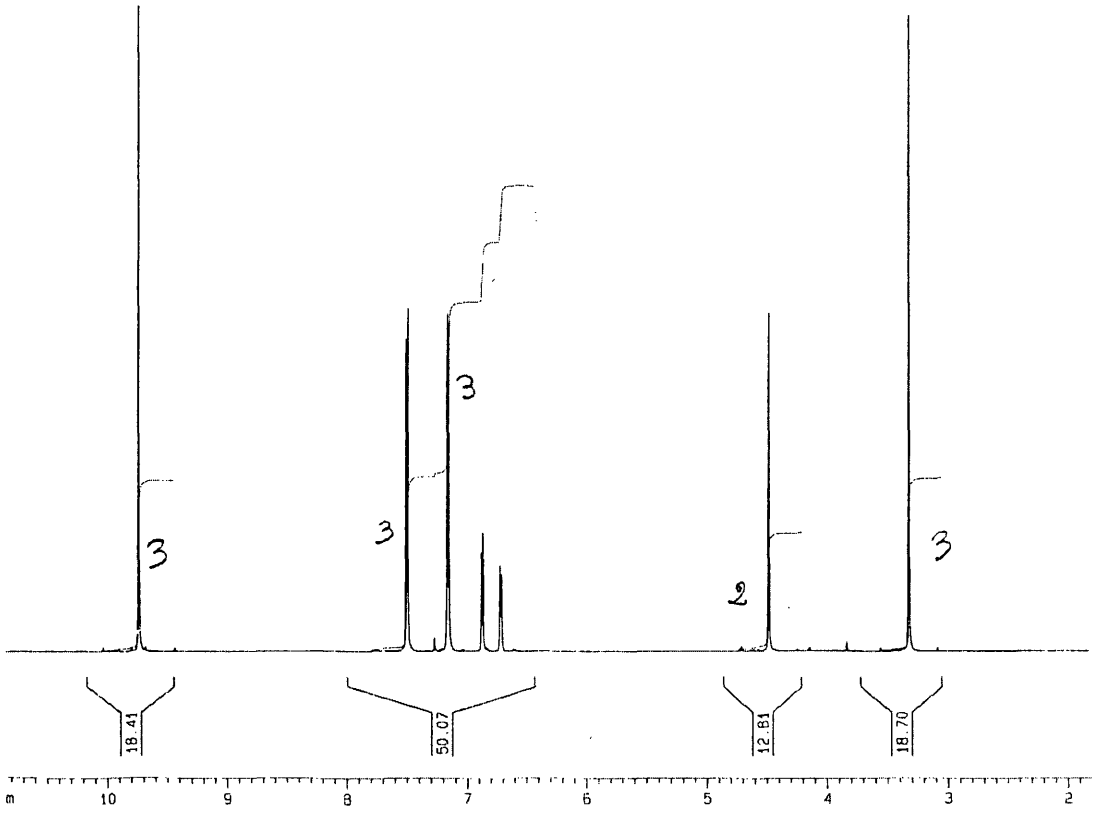
Annexes

Section 2.3.2.3: ^{1}H NMR spectrum of the unknown compound



Typical calculation for palladium leaching levels in the final product

$D = (A \times 100)/mc = (5.4347 \times ppm)/mb$

= percentage of metal Pd(0) found in the final compound expressed in % from the ppm data

where

mb = $Pd(PPh_3)_4$ contained in the supported catalyst (mg)

mc = maximal amount of metal Pd(0) which could leach into a solution (mg)

r = percentage of metal Pd(0) in $Pd(PPh_3)_4$

$mc = r \times mb$

$Pd(PPh_3)_4 = 1155.56$ $r = 106.4/1155.56 = 0.092$

Pd(0) = 106.40

$A = (ppm \times 5)/1000$

= Palladium leaching found in the product expressed in mg from the ppm data

For example, atomic absorption result for Pd analysis is 1 ppm and assuming there is 17.4 mg of $Pd(PPh_3)_4$ in 174 mg of the supported catalyst, hence total amount of Pd(0) in solution (%) after performing a bead reaction is = $(5.4347 \times 1)/17.4 = 0.31\%$.

Palladium leaching was determined by extracting the product with 6 drops of aqua regia for 30 minutes, then after addition of deionised water (5 ml). The mixture is centrifuged and analyses of the solution were undertaken on a Perkin Elmer 1100B atomic absorption instrument in conjunction with a series of palladium standards.

Aqua regia is a mixture of 15 mL of concentrated HCl and 5 mL of concentrated nitric acid.

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